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Original Articles

GROWTH AND TRANSFORMATION OF THE MANDIBULAR JOINT IN THE RAT

I. NORMAL FEMALE RATS

DANIEL A. COLLINS, A.B., M.S., D.D.S., HERMANN BECKS, M.D., D.D.S., MIRIAM E. SIMPSON, PH.D., M.D., AND HERBERT M. EVANS, M.D.

THE importance of the pituitary in the molding of the lower jaw has been recognized for many years due to the marked changes which occur in this region in acromegaly. There results a protrusion of the lower jaw which, like other cases of mandibular prognathism, presents a particular problem to the dentist.

This series of papers on the mandibular joint is an outgrowth of animal experimentation on the effects of pituitary growth hormone and thyroxin on skeletal tissues in hypophysectomized rats. The first in this series deals with the changes and transformation in the normal mandibular joint and establishes standards for comparison with the second part, which deals with the effect of removal of the pituitary gland, and the third part, which deals with replacement therapy with growth hormone and thyroxin in hypophysectomized rats.

In regard to the growth and transformation of the mandible, opinions differ as to the relative importance of endochondral and intramembranous bone formation.[2, 4, 5, 7, 9-13] With the exception of a treatise by Cabrini and Erausquin[3] little, if any, information is available on the histogenesis and morphogenesis of the mandibular joint in the rat.

From the Division of Dental Medicine, College of Dentistry, the George Williams Hooper Foundation for Medical Research and the Institute of Experimental Biology, University of California, San Francisco, and Berkeley, California.

Aided by grants from the American Foundation for Dental Science, the Research Board of the University of California, the Rockefeller Foundation, New York City, the California State Dental Association, the W. K. Kellogg Foundation, and Meharry Medical College.

It is certain that in the formation of the ramus of the mandible, to which particular attention is devoted in this paper, osseous replacement of a preexisting cartilage model is of great importance. The process, however, differs definitely from that observed in the growth of long bones. In the ossification of long bones, such as the tibia, the original ossification takes place in the center of the cartilage model and gradually encroaches upon the epiphysis. A secondary center of ossification appears in the epiphysis so that finally only a plate of cartilage is left between epiphysis and diaphysis. This cartilage, too, is eventually replaced by osseous tissue, preventing further increase in length of the bone. In the rat, a few cartilage cells remain in the epiphyseal plate (proximal) until late in life. The only other cartilage remaining is that which covers the articular surfaces of the extremities of the bone. In the condyloid process of the mandible, on the other hand, no secondary center of ossification appears. The cartilage is gradually replaced until only that at the articular end of the bone is left. This cartilage does not actually form the articular surface of the condyle as it is separated from the fossa by a fibrous covering.

EXPERIMENTAL MATERIAL AND RESULTS

Sixty-nine normal female rats of the Long-Evans strain, reared on an adequate diet,* were sacrificed at intervals between the ages of 5 and 465 days.† The right mandibular joint was roentgenographed, decalcified, sectioned, and stained with hematoxylin and eosin.

In the strict sense, the rat has no "temporo-mandibular joint" because the articulation of the mandibular condyle is with the squamosal.[6] It is, therefore, actually a "squamoso-mandibular joint." The term squamoso-mandibular joint has not been used, but simply mandibular joint, in order not to introduce confusion into the literature, since the term temporomandibular joint is correctly used for other species.

In the rat, as in man, the mandibular articulation is a ginglymoarthrodial joint. This type of joint allows ample hinge action for use of the molars in grinding, also gliding action for gnawing with the incisors. A brief description of the gross anatomy and physiology of the articulation in the normal adult female rat is included.

The articular surface of the squamosal or cranial portion of the joint, the interarticular soft tissues, and the articular surface of the ramus or mandibular portion will be described in the order named.

1. The cranial portion of the joint‡ is formed by an elongated groove in the squamosal bone. The long axis of the groove lies in the anteroposterior plane and is directed upward and backward. The fossa faces downward and backward. It is divided into an anterior and a posterior part by a rounded eminence which is continuous with the zygomatic process of the squamosal. The part of the fossa posterior to this eminence accommodates the condyle of the mandible when the molars are being used in chewing. That part of the fossa anterior to the eminence accommodates the condyle of the mandible when the incisors are being used in gnawing. The eminence not only divides the fossa into two parts, but also divides

*Diet XIV consists of 68.5 per cent whole wheat, 5 per cent casein, 10 per cent fish meal, 10 per cent alfalfa leaf meal, 1.5 per cent NaCl, and 5 per cent fish oil.

†Numbers of rats studied at each age level were as follows: 3 at 5 days, 4 at 10 days, 3 at 20 days, 3 at 25 days, 7 at 27 to 28 days, 4 at 30 days, 6 at 35 to 40 days, 3 at 45 days, 4 at 50 days, 4 at 65 to 68 days, 2 at 72 days, 5 at 105 to 106 days, 5 at 119 to 141 days, 3 at 151 to 175 days, 4 at 195 to 215 days, 2 at 251 to 258 days, 2 at 300 to 307 days, 1 at 449 days, and 1 at 465 days.

‡For purposes of anatomical description the rat is described in its normal horizontal position. The following terms are, therefore, considered equivalent: posterior and caudal; anterior and cephalad; inferior and ventral; superior and dorsal.

it into two levels. The inferior part is approximately in the plane with the lower part of the eminence and the superior part is in that of the upper part of the eminence.

2. The interarticular soft tissues are composed of:

a. The synovial membrane which covers the articular surface of the fossa and is composed of fibrous tissue which is continuous with the periosteum at the periphery of the fossa.

b. The interarticular disc, which is a comparatively thick plate of fibrous tissue, conforms to the configuration of the fossa and the condyle. Its inferior concave surface is in contact with the condyle; its superior convex surface is in contact with the glenoid fossa. It is thicker at the margin than at the center.

c. The synovial membrane which covers the condyle and is composed of a layer of fibrous tissue. It adheres to the cartilage of the condyle and is continuous with the periosteum.

3. The mandibular portion of the joint, formed by the condyloid process, consists of two parts; the condyle and the constricted portion which supports it, the neck. The condyle presents a surface for articulation with the articular disk of the joint. The anteroposteriorly directed long axis of the condylar head in the rat is, in the adult, approximately twice the length of the short axis. (This is in contrast to the position of the long and short axes of the condyle in man.) The neck is flattened from side to side and is strengthened by ridges which descend from the anterior and posterior borders as well as the sides of the condyle. The thickest of these ridges extends from the lateral side of the condyle to the base of the lower incisor.

The mandibular joint in the rat, as in other rodents, is adapted for gnawing or cutting with the large incisors. In this animal the incisors erupt continuously throughout life, replacing the tooth structure of the incisal edge which is being ground away. In performing this action, the condyle moves downward and forward into the anterior (longer) half of the fossa. The lower jaw is protruded until the incisors meet. The lower incisor may be occluded either posteriorly or anteriorly to the upper incisor. This type of action allows for use of the enamel covering the labial surface of the lower incisor against the dentine which forms the lingual surface of the upper incisor or the reverse. In chewing with the molars the condyle moves backward and upward into the posterior (shorter half) of the glenoid fossa. This part of the fossa is shallow and is, therefore, better adapted for the movement of the jaw necessary in use of the molars.

The histologic sections of the mandibular joint were made in the mediolateral direction and in the vertical plane, as demonstrated in Fig. 1. Due to differences in the age at which changes occur in the cranial portion, in the interarticular soft tissue, and in the mandibular portion of the joint, these parts will be discussed separately and in the order mentioned.

The *cranial portion* of the joint is primarily membranous bone. A cartilage-like mass of tissue, however, lies adjacent to the articular surface of the fossa, separated from the joint cavity only by a thin layer of fibrous tissue. This tissue, as seen in the 5-day-old rat, is illustrated in Fig. 2. With increasing age, this modified tissue expands and continues to conform to the changing shape of the condyle. The growth of the fossa is rapid up to approximately 45 days of age (Figs. 3 to 8); after this age the growth rate is greatly reduced (Fig. 9) and by 106 days of age (Fig. 10) growth has almost ceased. Calcification of the cartilage-like tissue occurs in older animals, but even in old age, 465 days, the tissue can still be distinguished. The persistence of this tissue is probably related to the continued capacity of the fossa to be remodeled to parallel any change in shape of the condyle arising from unusual stresses either physiologic or pathologic. The bone forming the fossa becomes very dense in the old rat and marrow spaces become greatly restricted.

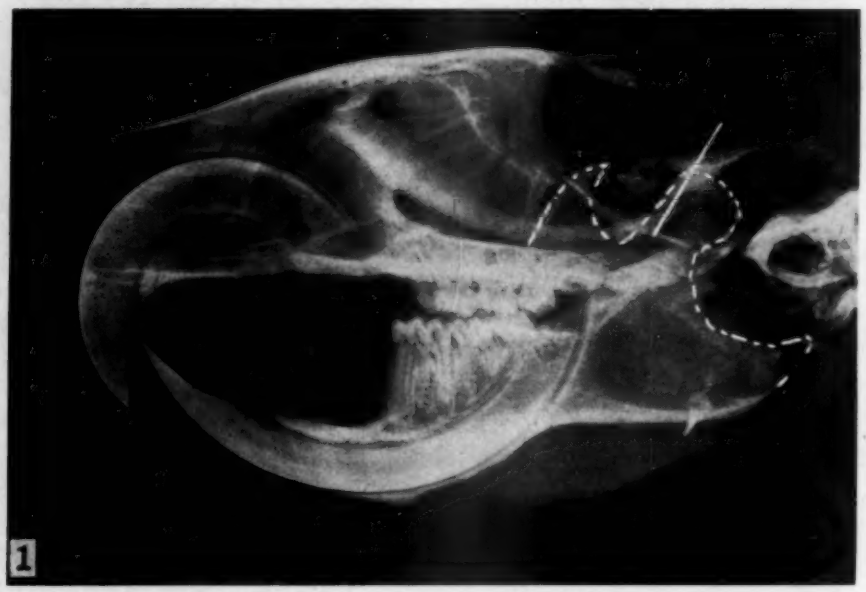

Fig. 1.—Skull roentgenogram of a normal adult rat; aged 253 days at autopsy. (Four times natural size.) (Pl. 6321.)

Mediolateral sections of the mandibular joint in normal rats, cut in the vertical plane (as indicated in Fig. 1). Hematoxylin and eosin stain, 8 to 10 micra. With the exception of Fig. 6, all photomicrographs are of the same magnification: Homal VI, objective 6, extension 66 cm., ×92.

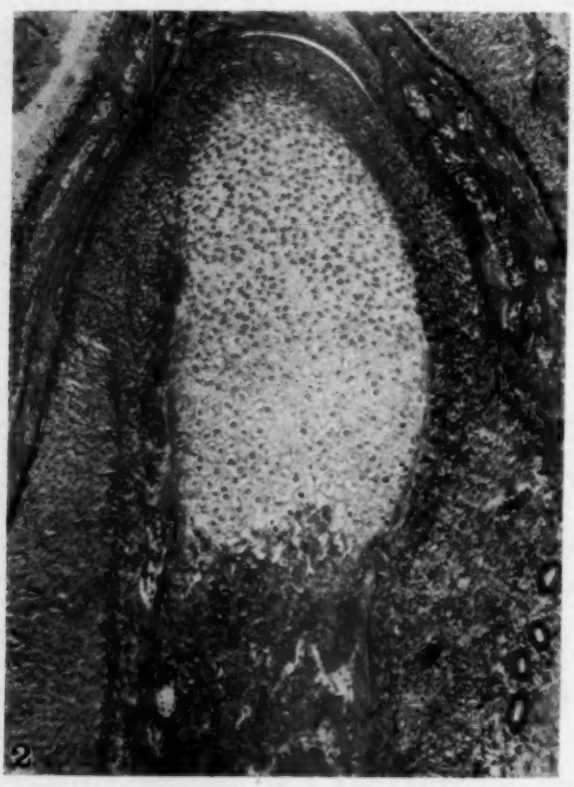

Fig. 2.—Age, 5 days. (Sp. 8700, Pl. 8518.)

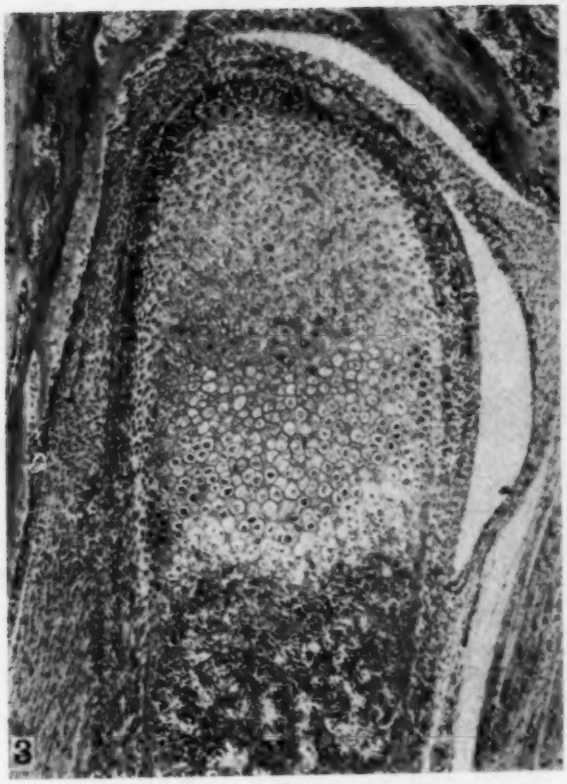

Fig. 3.—Age, 10 days. (Sp. 8388, Pl. 8519.)

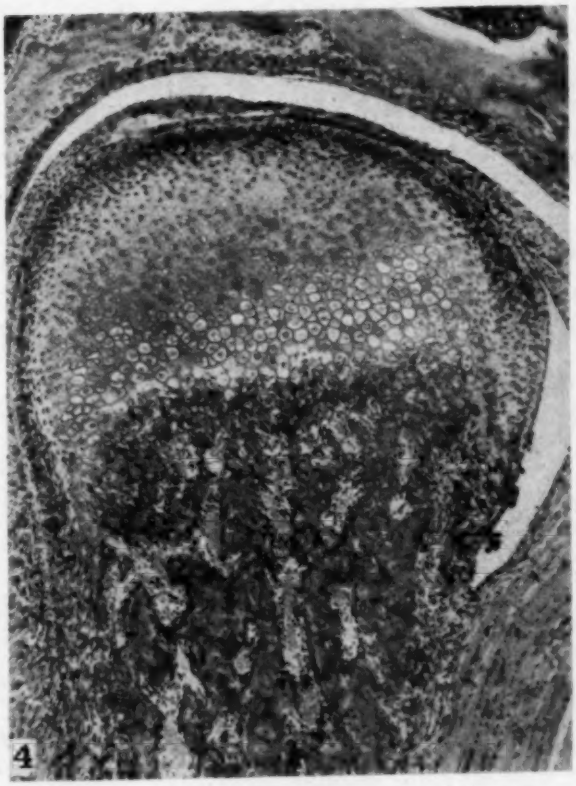

Fig. 4.—Age, 20 days. (Sp. 8706, Pl. 8521.)

The *synovial membranes and the articular discs* of young animals (Figs. 2 to 6, 5 to 25 days) are still quite rich in cells but by 72 days of age (Fig. 9) the fibrocytes begin to flatten and are imbedded in dense fibers. No further changes were observed in these tissues after approximately 106 days of age (Fig. 10).

In the mandibular portion at 5 days of age, the youngest rat studied, ossification of the condyloid process was well advanced; however, the condyle was still composed of cartilage. The condyloid process of the mandible from 5 to 20 days of age is narrow and conical in shape and is composed wholly of hyaline cartilage (Figs. 2 to 5). The cartilage is separated from the joint by a layer of fibrous connective tissue which constitutes the synovial membrane. Near the articular surface the cartilage cells are flattened. Deeper in the cartilage the chondrocytes are rounded and enlarged. The individual cells are separated by large amounts of matrix. The cells are arranged in groups of two, and are usually flattened at the surface of contact. Near the line of erosion, the cells are arranged in rows, the rows being separated by scanty matrix. Nuclei in this region show karyolytic degeneration and the cytoplasm is vacuolated. These cells are obviously being eroded by the advancing osteogenic tissue.

Osteogenesis is active at the zone of erosion as indicated by the abundant vessels and by the number and size of osteoblasts. Numerous delicate trabeculae of bone are being formed, having as a core the remains of the vacuolated cartilage cells and cartilage matrix. A dense palisade of osteoblasts surrounds the trabeculae of this primary spongiosa. Osteoclasts are frequently present, especially in those sites where the new formed trabeculae are adjacent to the cortical bone. By 20 days of age the trabeculae continuous with the cartilage have become much coarser. They are not resorbed in the center of the shaft as they are in the tibia leaving a large marrow cavity. The marrow of the mandibular ramus becomes restricted from an early age to fairly narrow channels. The ramus of the mandible is being increased in width and thickness by both endosteal and periosteal bone formation, as indicated by rows of cuboidal osteoblasts aligned both on the inside and outside of the cortical plate and on the surface of the trabeculae.

By 25 days of age the diameter of the condyle has greatly increased, but the width of cartilage capping it has decreased (Fig. 5). After this age the reduction in width of the cartilage is more gradual. The cartilage by 25 days of age shows three distinct zones (Fig. 6). Just beneath the fibrous covering of the condyle there is a superficial zone of flattened cells (embryonic zone), the long axis of the cells being arranged parallel to the articular surface. In the second (intermediate) zone the cells are enlarged and become rounded. They are separated by small amounts of matrix. The cartilage cells here are more clearly outlined. The third zone is characterized by a vacuolization of the chondrocytes (vesicular zone). The cells are now elongated perpendicular to the articular surface. Almost no matrix is present between the vacuolated cells (zone of erosion). These zones are similar to those in the epiphyseal cartilage plate of the growing tibia except that the cells of the intermediate zone are not flattened or arranged in columns.[1, 8]

A

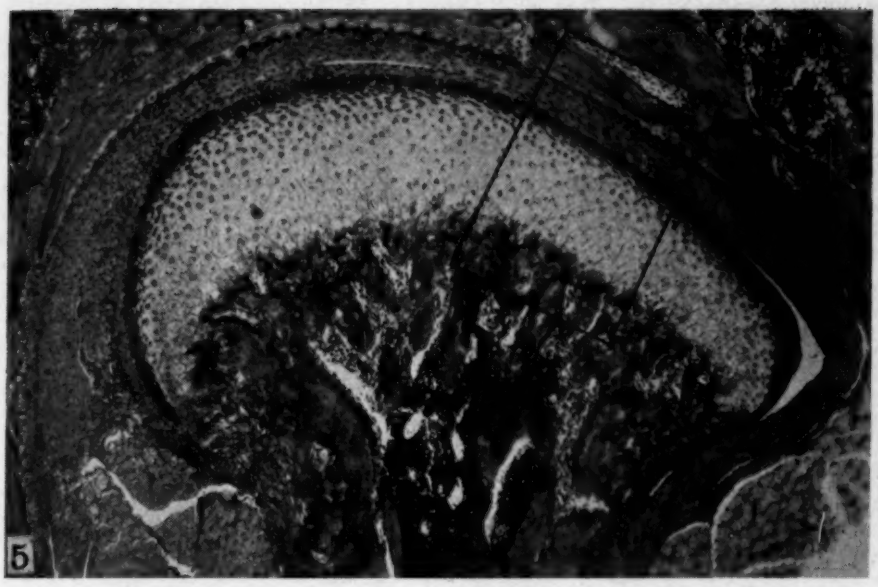

Fig. 5.—Age, 25 days. (Sp. 8709, Pl. 8522.)

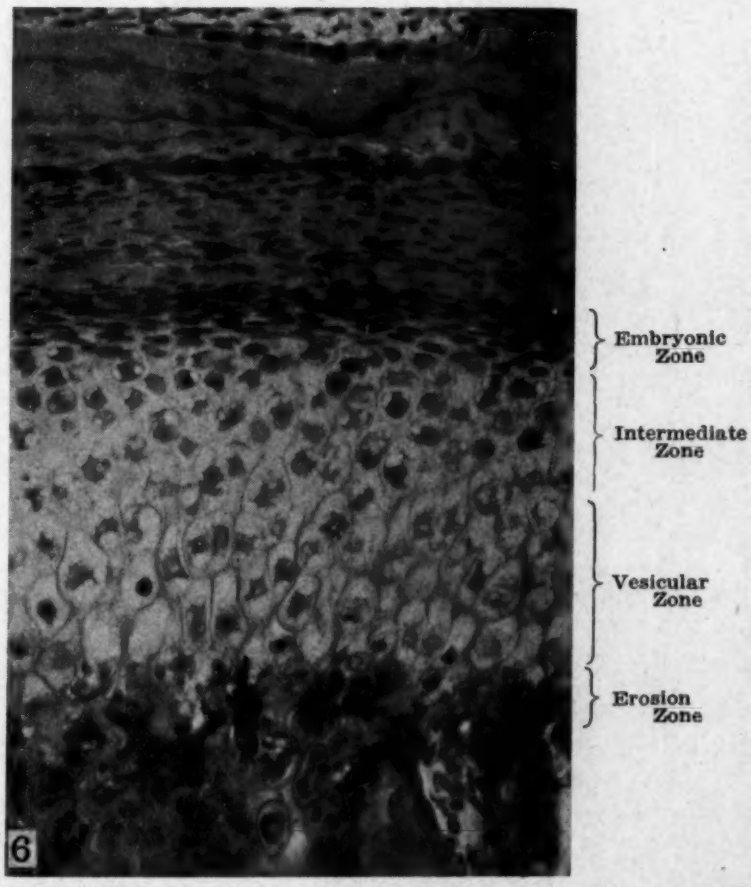

Fig. 6.—Age, 25 days. Higher magnification of *A* in Fig. 5. (Homal VI, objective 20, extension 66 cm., ×325). (Pl. 8555.)

By 30 days of age (Fig. 7) the condyle of the mandible no longer consists primarily of cartilage. The condyle has increased in size, and the cartilage has been largely replaced as bone was formed. The cartilage is restricted to a thin band covering the condyloid process. The cartilage now shows an increase in amount of matrix and decreased cell size. Calcification of the vesicular zone is first indicated at this age by changed staining reaction. There is also evidence of reduction in the intensity of osteogenesis. The capillaries of the zone of erosion are reduced in number. Blood-forming cells are now more numerous in the marrow and extend closer to the zone of erosion, whereas earlier this area was occupied chiefly by vascular tissue and osteoblasts. The marrow spaces have been further restricted due to increased size and fusion of the trabeculae.

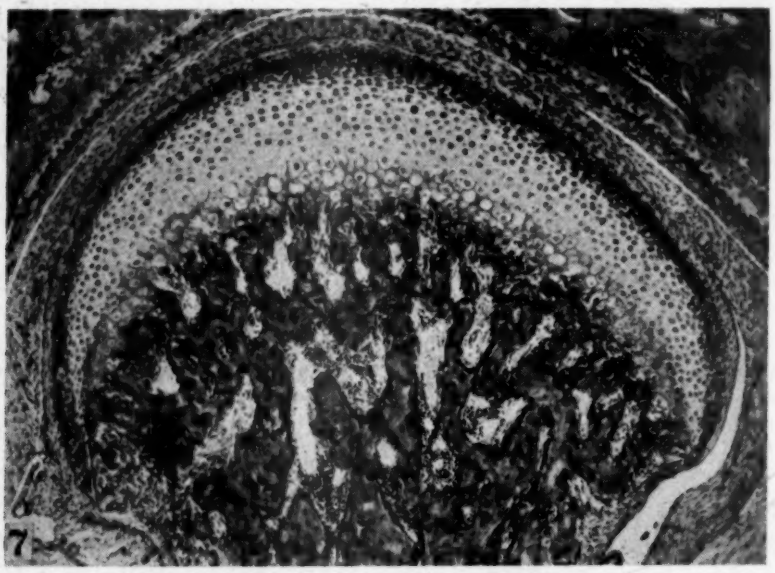

Fig. 7.—Age, 30 days. (Sp. 6755, Pl. 8420.)

By 45 days of age (Fig. 8) chondrogenesis and osteogenesis are definitely slowed. The cartilage shows evidence of decreased activity; more matrix is present in both the intermediate zone and in the zone next to the marrow. The cells of these zones have not enlarged as greatly as at earlier ages and little or no vacuolation is now seen. Coarse trabeculae now extend up to the cartilage so that the area of contact between marrow and cartilage is reduced.

At 72 days of age (Fig. 9) the vascular elements come in contact with cartilage in only a limited number of places. There is evidence of beginning calcification of the cartilage, and formation of bone on the surface of the cartilage between trabeculae. Due to the thickening and fusion of the trabeculae the marrow spaces are becoming very restricted and the ramus is rapidly coming to be formed of almost solid bone. Haversian systems are being formed in this bone. The progressive calcification of the cartilage, the consolidation of the trabeculae, and Haversian system formation are illustrated in Figs. 10 and 11, representing the condition in 106- and 258-day-old rats, respectively. The

progressive reduction in size and number of osteoblasts in the periosteum is illustrated in these figures.

Continuation of the progressive senile changes described in the fore-going paragraphs results in the condition which is seen in the 449-day-old rat (Fig. 12). The oldest normal rat studied (465 days) showed little change beyond that

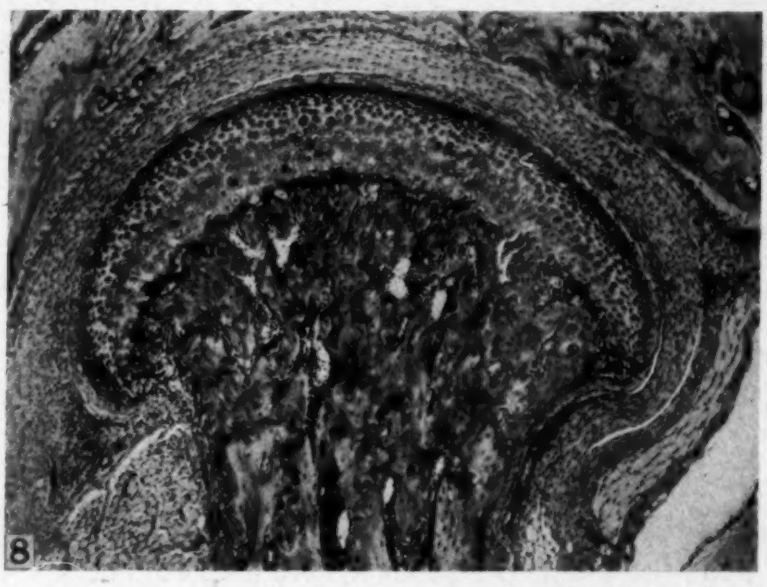

Fig. 8.—Age, 45 days. (Sp. 8726, Pl. 8526.)

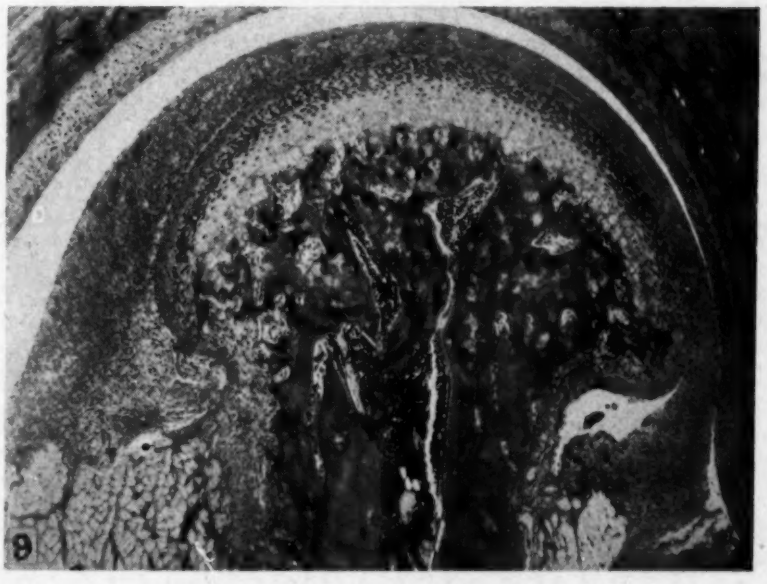

Fig. 9.—Age, 72 days. (Sp. 8088, Pl. 8199.)

illustrated in Fig. 12. In such old rats the bone of the condyle is extremely dense. Occasional osteoblasts are recognizable on the surface of the trabeculae. The condition in the human being seems to be comparable to that in the rat;

Weinmann[13] reported continued formation of bone in the mandible late in life, and Vaughan[11] observed that the condyle continues to change in form throughout life. One observation made here on the human mandible may also be cited. The condyle of the mandible of an 80-year-old man still showed nests of cartilage cells remaining near the articular surface of the condyle.

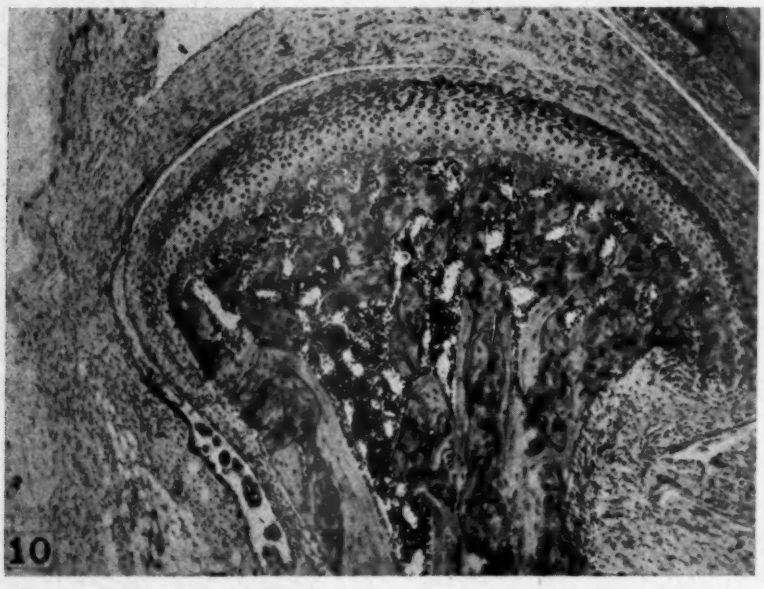

Fig. 10.—Age, 106 days. (Sp. 7038, Pl. 8379.)

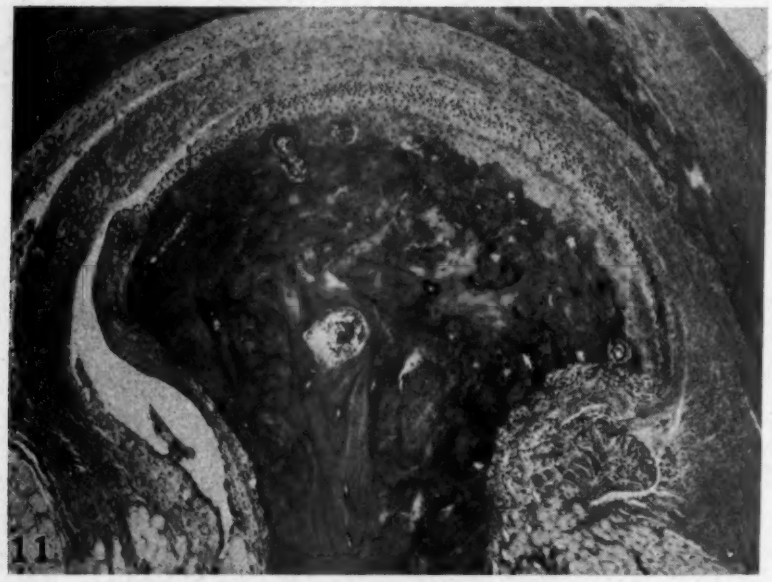

Fig. 11.—Age, 258 days. (Sp. 8379, Pl. 8202.)

The process of calcification of the cartilage, although involving the vesicular and intermediate zones, does not reach the embryonic zone. A definite line of demarcation marks the junction of the former two zones with the latter zone.

The condition should be compared with that at the proximal end of the tibia as described by Becks, et al.[1] The condition in the tibia is similar to that in the condyle of the mandible at 5 days of age. After this age a secondary center of ossification appears in the head of the tibia and an epiphyseal cartilage plate is formed. Cartilage cells remain in this plate, though sealed from the marrow until old age; cartilage also survives on the articular surface of this bone. In the condyle of the mandible no secondary center of ossification appears. Instead, the cartilage at the surface of the condyle remains. This arrangement of cartilage tissue allows for remolding in form to accommodate chewing habits, muscle pull, malocclusion, and other extrinsic factors which are recognized as important in the development of the mandible and temporomandibular articulation.[11, 14] Due to the persistence of the embryonic cartilage cells in the condyle, there remains a possibility of reactivation of growth and remodeling of the ramus of the mandible of the rat.

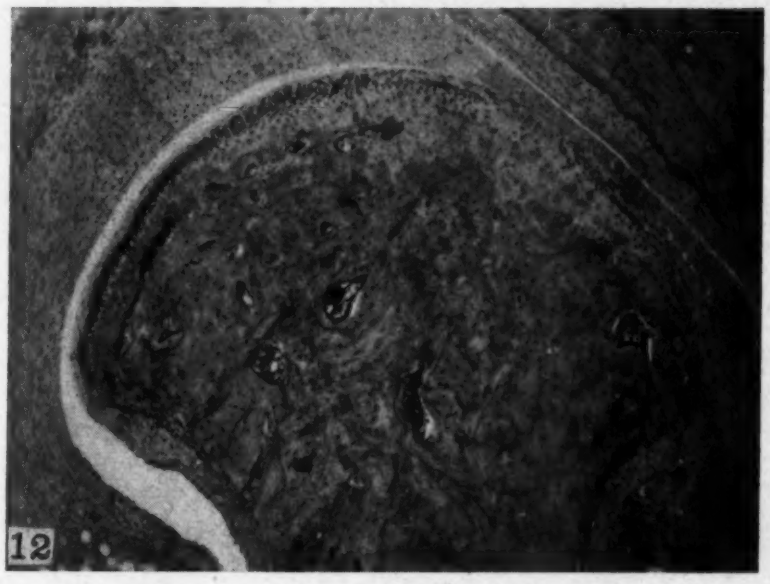

Fig. 12.—Age, 449 days. (Sp. 8367, Pl. 8391.)

SUMMARY AND CONCLUSIONS

Growth and transformation of the mandibular joint in the normal rat from 5 to 465 days of age is described. The marked changes which occur in the fossa, interarticular soft tissue, and the condyle and the changes associated with progressively decreased growth activity of this region are described and illustrated.

The bone forming the fossa is formed primarily from intramembranous ossification. A layer of cartilage-like tissue lies subjacent to the articular surface of the fossa; complete calcification of this tissue does not occur. The continued presence of this cartilage-like tissue probably accounts for the capacity of the fossa to adapt throughout life to changing stresses.

The synovial membranes and interarticular disc become more fibrous and less cellular with advancing age.

The mandibular condyle in the very young rat (5 days old) is composed entirely of hyaline cartilage. This cartilage continues to grow but is also being eroded by encroachment from the center of ossification. By 25 days of age, four zones have been differentiated in the cartilage: (1) the zone of embryonic cells; (2) the intermediate zone: (3) the zone of vacuolated cells; (5) the zone of erosion. In old animals the latter three zones disappear or become calcified. The zone of embryonic cells remains uncalcified up to 465 days of age.

The trabeculae, which are thin and delicate in the younger rats, become progressively coarse and fuse with advancing age. Only small islands of marrow remain in the dense bone of the ramus by 250 days of age. The cartilage in contact with the fused trabeculae is calcified.

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GROWTH AND TRANSFORMATION OF THE MANDIBULAR JOINT IN THE RAT

II. Hypophysectomized Female Rats

Daniel A. Collins, A.B., M.S., D.D.S., Hermann Becks, M.D., D.D.S., Miriam E. Simpson, Ph.D., M.D., and Herbert M. Evans, M.D.

THERE is no report available on the effects of hypophysectomy on the growth and transformation of the mandibular joint of the rat. In order to establish standards for comparison of the effects of growth hormone and thyroxin[4] on the mandibular joint of the hypophysectomized rat, it was necessary to study the development of this articulation in rats whose pituitary glands had been removed. The development of the mandibular joint in the normal female rat has already been reported.[3]

The rats used were of the Long-Evans strain. They were raised on the same diet as the normal animals (see Paper I) supplemented daily by a wet mash of diet I* following hypophysectomy. The method of operation was a modification of the Smith parapharyngeal approach. Only those animals are discussed in this paper in which the characteristics of hypophysectomized rats were already obvious during life, and in which the completeness of the operation was confirmed at autopsy by the finding of a sella turcica free of pituitary fragments. These same animals were used for studies of the tibia, and the experimental conditions have been described elsewhere in detail.[2]

Seventy-nine female rats were hypophysectomized at 23 to 30 days of age and were autopsied at different intervals after the operation† to determine the progressive changes in the mandibular articulation at intervals ranging 4 to 645 days after hypophysectomy. The mandibular fossa, interarticular soft tissues, and condyloid process of the mandible will be described.

Four days after hypophysectomy (Fig. 1) the bone forming the *mandibular fossa* already shows changes comparable to those in aging animals. It is denser, the cartilage-like tissue lining the articular surface is calcified and already comparable to that in a normal rat twice the chronological age (65 days of age; see Paper I). Eighteen days after the operation (Fig. 2) the senile changes in

From the Division of Dental Medicine, College of Dentistry, the George Williams Hooper Foundation for Medical Research and the Institute of Experimental Biology, University of California, San Francisco, and Berkeley, California.

Aided by grants from the American Foundation for Dental Science, the Research Board of the University of California, The Rockefeller Foundation, New York City, the California State Dental Association, the W. K. Kellogg Foundation, and Meharry Medical College.

*Diet I, slightly modified from McCollum's formula, consists of 67.5% whole wheat, 15% casein, 10% whole milk powder, 0.75% NaCl, 1.5% $CaCO_3$, 5.25% hydrogenated vegetable oil, and a concentrate of fish oil in amount to give 19 U.S.P. units of vitamin A and 2.5 A.O.A.C. chick units of vitamin D per gram of diet.

†Numbers of rats studied at different postoperative intervals were as follows: 2 at 4 days postoperative, 4 each at 6, 8, 10, and 12 days, 2 at 18 days, 3 from 28 to 30 days, 4 from 37 to 43 days, 4 from 52 to 60 days, 6 from 87 to 91 days, 5 from 100 to 132 days, 5 from 145 to 167 days, 6 from 206 to 279 days, 10 from 326 to 353 days, 5 from 389 to 403 days, 1 at 445 days, 3 from 512 to 546 days, 4 from 561 to 574 days, 3 from 617 to 645 days.

the tissues of the fossa are similar to those described for the 106-day-old normal rat. Twenty-eight days after hypophysectomy (Fig. 3) the fossa is comparable structurally to that of 465-day-old normal rat, but is smaller. The bone is dense and only small islets of marrow tissue remain.

In the *interarticular soft tissue* the major changes resulting from hypophysectomy are diminution in cell size and increase in its fibrous intercellular substance. This increase in fibers is recognizable within twenty-eight days after the operation (Fig. 3).

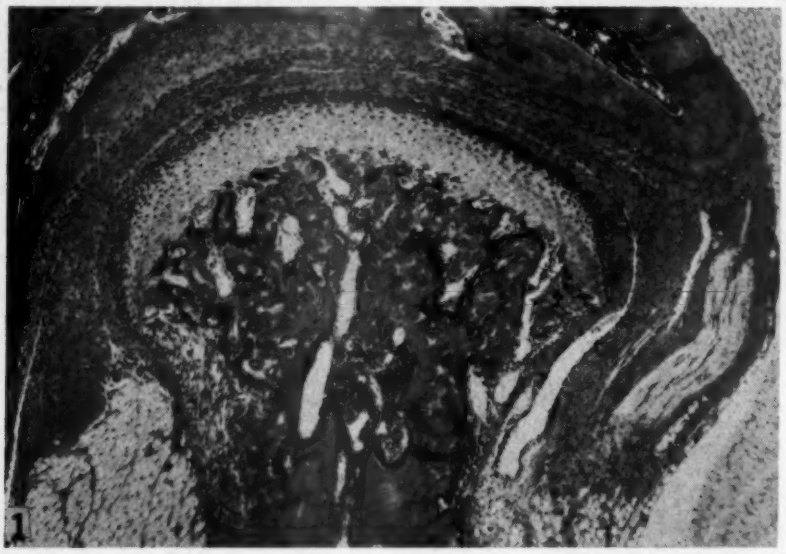

Fig. 1.—Postoperative interval 4 days. (Age at hypophysectomy, 26 days.) (Sp. 6748, Pl. 8418.)

Figs. 1 to 4.—Mediolateral sections of the mandibular joint in hypophysectomized rats, cut in the vertical plane (as indicated in Fig. 1 of the first paper of this series). Hematoxylin and eosin stain, 8 to 10 micra. All photomicrographs are of the same magnification: Homal VI, objective 6, extension 66 cm., ×92.

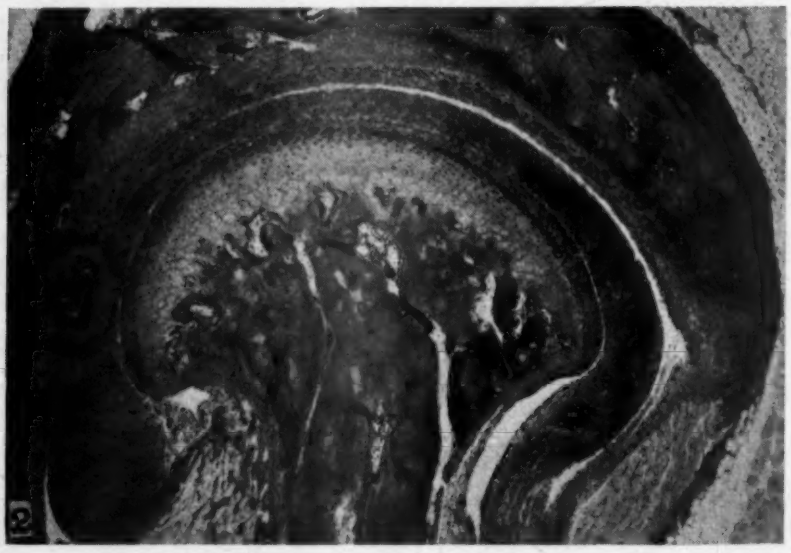

Fig. 2.—Postoperative interval 18 days. (Age at hypophysectomy, 27 days.) (Sp. 6630, Pl. 8394.)

In the *condyloid process* (Fig. 1) changes have occurred within four days after the operation; the morphology in such animals, chronologically 30 days of age, is similar to that of the normal rat of 45 days of age. Chondrogenesis and ossification are markedly reduced in comparison with normal rats of equivalent chronological age. The bony trabeculae extending from the cartilage into the marrow are already coarse.

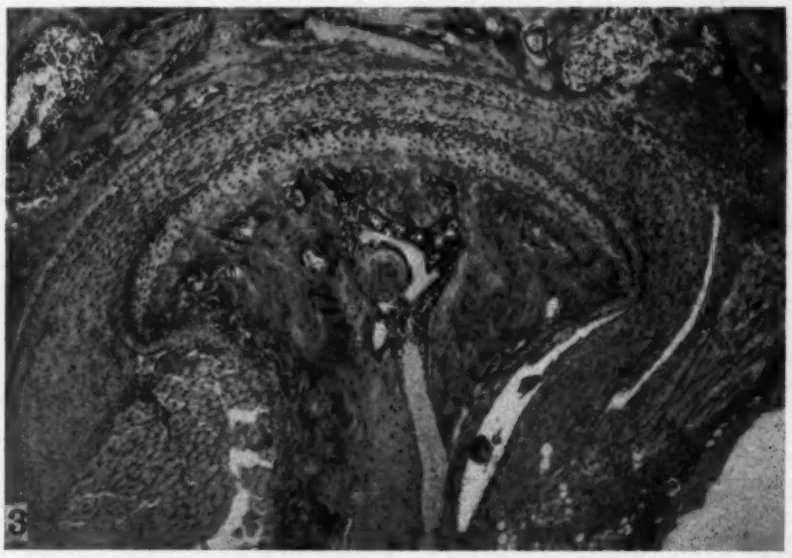

Fig. 3.—Postoperative interval 28 days. (Age at hypophysectomy, 27 days.) (Sp. 8369, Pl. 8403.)

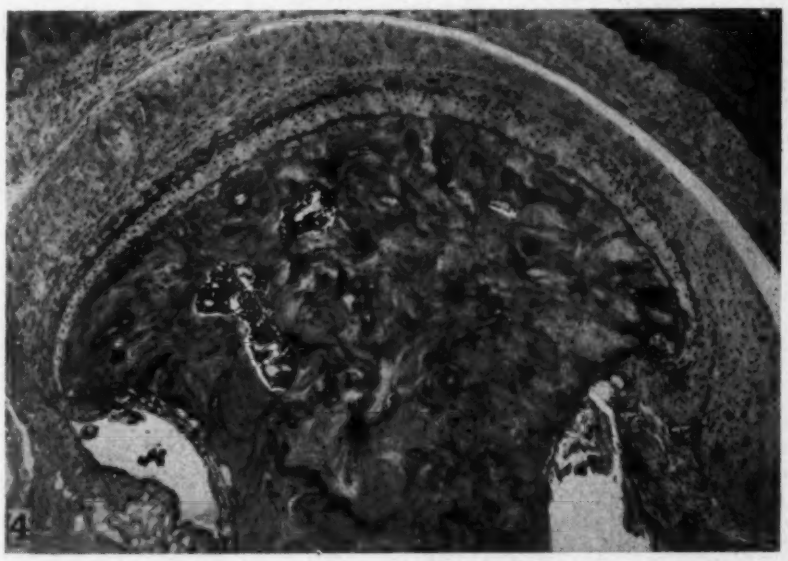

Fig. 4.—Postoperative interval 639 days. (Age at hypophysectomy, 29 days.) (Sp. 7869, Pl. 8438.)

The width of the condyloid cartilage remains fairly constant for the first eighteen days following operation (Fig. 2). The chondrocytes are reduced in size and the intercellular substance has increased. The latter shows calcification extending throughout the vesicular zone and well into the intermediate

zone. Very little change is observed in the zone of embryonic cells. Erosion of cartilage and formation of new trabeculae has ceased; endosteal ossification on the surface of the trabeculae is apparently not seriously affected, and has resulted in a thickening of the trabeculae. The increased density of the bone of the ramus is associated with a decrease in marrow space. The remaining marrow is still quite vascular. The condition seen in the condyle of the mandible twenty-eight days after the operation (Fig. 3), in animals of 56 days chronological age, is comparable to that attained at 258 days by a normal rat. The line of demarcation between the calcified cartilage (chiefly the old zone of vesiculated cells) and the uncalcified cartilage is much sharper than in the older normal animal.

Some intensification of these changes occurs after longer postoperative periods. The condition after the longest postoperative period observed, 645 days, is shown in Fig. 4. It will be noted that the condyle is now composed of dense bone except for a few small isolated marrow cavities. The few remaining cartilage cells are widely separated by the calcified matrix. Calcification of the cartilage has progressed well into the intermediate zone.

These changes are somewhat different from those observed in the shaft of the tibia after long postoperative intervals.[2] In the tibia, as in the mandible, no new trabeculae are formed after hypophysectomy. In the tibia however, most of those present are resorbed. Only a few coarse trabeculae extend from the epiphyseal cartilage into the marrow; other than these trabeculae the diaphysis is almost devoid of bone aside from the thin cortical bone. In the condyle of the mandible the resorption of trabeculae does not occur; on the contrary, they become increasingly coarser and fuse until only a few vascular marrow channels are left permeating the solid bone.

SUMMARY

The mandibular joint was studied in 79 hypophysectomized female rats at postoperative intervals ranging from 4 to 645 days. The transformations occurring following hypophysectomy are similar to those occurring in aging rats. The changes occur, however, very much earlier in the hypophysectomized rat; chondrogenesis is considerably slowed within four days after the operation. The ossification of the mandible of the hypophysectomized rat by twenty-eight days after operation is as advanced as in a 258-day-old normal rat. As in the normal rat some uncalcified cartilage remains in the condyle for long periods. The persistence of this tissue confers upon this joint the continued capacity for growth and remodeling.

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GROWTH AND TRANSFORMATION OF THE MANDIBULAR JOINT IN THE RAT

III. The Effect of Growth Hormone and Thyroxin Injections in Hypophysectomized Female Rats

Hermann Becks, M.D., D.D.S., Daniel A. Collins, A.B., M.S., D.D.S., Miriam E. Simpson, Ph.D., M.D., and Herbert M. Evans, M.D.

THE mechanism of production of mandibular prognathism as it occurs in extreme form in acromegaly has not been carefully analyzed. It has been postulated that the condyle in the adult still possesses potentiality of growth, and Sicher[4] has recently suggested that overproduction of growth hormone by pituitary tumors might be responsible for prognathism. It is possible to test this hypothesis by studying the mandibular joint of animals treated with growth hormone.

The hypophysectomized rat is an excellent test animal for such a study. Rats which had been hypophysectomized at 26 to 30 days of age and maintained for long periods (283-502 days) were available for such a study. A portion of these animals were injected with growth hormone.* As thyroxin is also important in growth and differentiation of the skeletal system, thyroxin alone and in combination with growth hormone was also injected. A total of 27 animals was placed in these injected groups, and 10 were reserved as controls. The more detailed description of the experimental conditions is given in the paper in which osteogenesis in the tibia is described[5] (see Table 3 and Fig. 1). The conditions of osteogenesis in the mandibular joint in normal rats of different ages and in hypophysectomized rats at different postoperative periods have been described in Papers I and II of this series on the mandibular joint.[6, 7]

Hypophysectomized Control.—The hypophysectomized controls (10 rats) included animals of the same range of postoperative intervals as in experimental animals (see also Paper II). This area as in a hypophysectomized rat 272 days after the operation is given in Fig. 1. It is representative of the general condition of this joint at the time when injections were started. The condyle is completely ossified except for a few small marrow cavities and vascular channels. Calcification of the cartilage has progressed into the intermediate zone. Remnants of the embryonic zone, immediately subjacent to the synovial membrane,

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*The growth hormone injected[3] was pure by physicochemical criteria. The standardization of the preparation is given in the paper devoted to the osteogenesis of the tibia.[5]

are clearly visible (*A* in Fig. 1) but appear inactive. A sharply defined demarcation line indicates the extent to which calcification of the cartilage has progressed.

Injection of Growth Hormone.—Growth hormone alone in doses of 200 μg. daily for 39 days was administered to 10 rats. The postoperative range represented in this group is 283 to 433 days. The minimum response of these rats to the injection of pure growth hormone is shown in Fig. 2. It is designated "minimum response" because it was the narrowest cartilage observed in any of the rats of this group. In the bone which forms the fossa, a striking acceleration of osteogenesis is observed. The cartilage-like tissue lining the fossa shows a reactivation over the entire surface of the fossa. The width of this tissue is greater than that observed in the fossa of the normal rat at any age included in this study. The cells in the synovial membranes and articular disc have greatly increased in number. In the condyle, cartilage and bone growth is comparable to that seen in the young growing normal rat. The chondrocytes have increased in number and are separated only by small amounts of matrix.

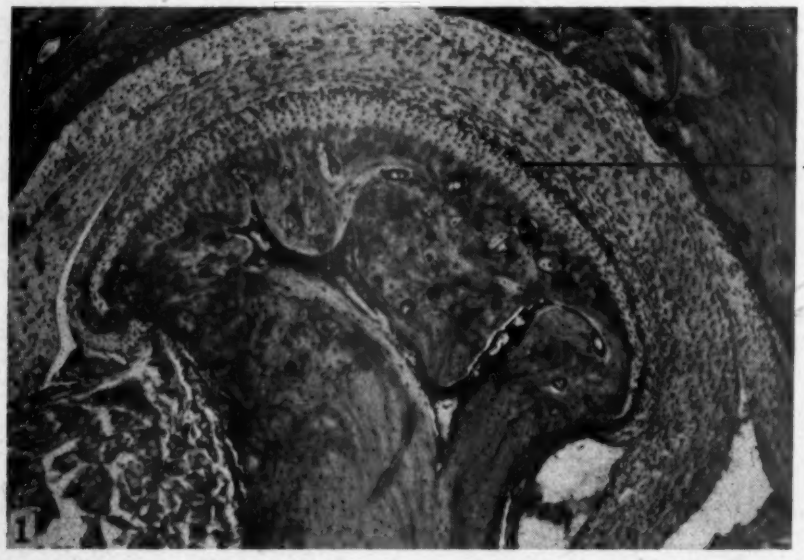

Fig. 1.—Uninjected control. Postoperative interval, 272 days. (Age at operation, 28 days.) (Sp. 8382, Pl. 8428.)

Figs. 1 to 5.—Mediolateral sections of the mandibular joint in hypophysectomized rats, cut in the vertical plane (as indicated in Fig. 1 of the first paper of this series). Hematoxylin and eosin stain, 8 to 10 micra. All photomicrographs are of the same magnification: Homal VI, objective 6, extension 66 cm., ×92.

The "maximum response" to pure growth hormone injections is shown in Fig. 3. The difference between the minimum and maximum response is chiefly in the width of the cartilage. Marked stimulation of both chondrogenesis and osteogenesis are present. Cartilage cells are clearly aligned in rows, especially in the zones of enlarged and vesicular cells. In the primary spongiosa the number of vascular loops and of osteoblasts is comparable to that in the 20-day-old normal rat. The dense bone characteristic of the senile condyle is being rapidly resorbed and replaced by delicate trabeculae.

Injections of Thyroxin.—The group of rats injected with thyroxin included 8 animals with a postoperative range of 283 to 502 days. The dose of thyroxin daily for the first eight days was 7.5 μg. It was necessary to reduce this dose to 5 μg. for the remainding thirty-one days of the experiment due to the great

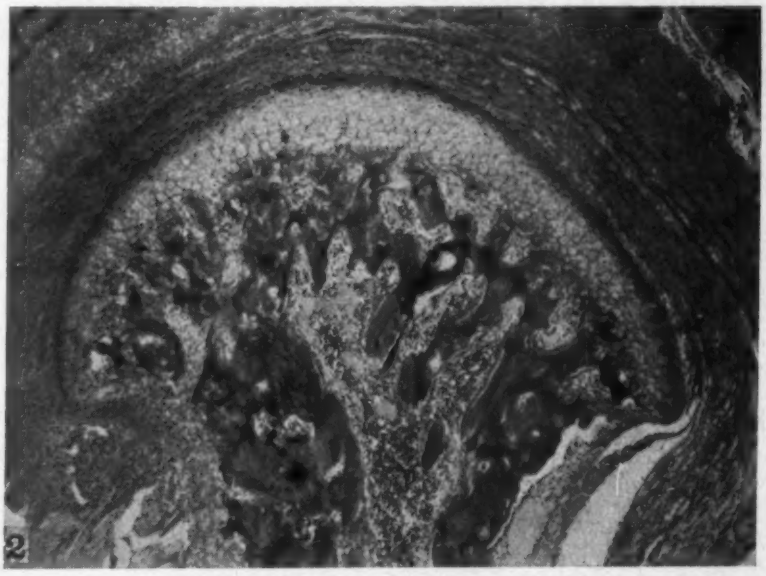

Fig. 2.—Minimum response to 39 days of growth hormone injections, begun after a postoperative interval of 292 days. (Age at operation, 28 days.) (Sp. 8777, Pl. 8541.)

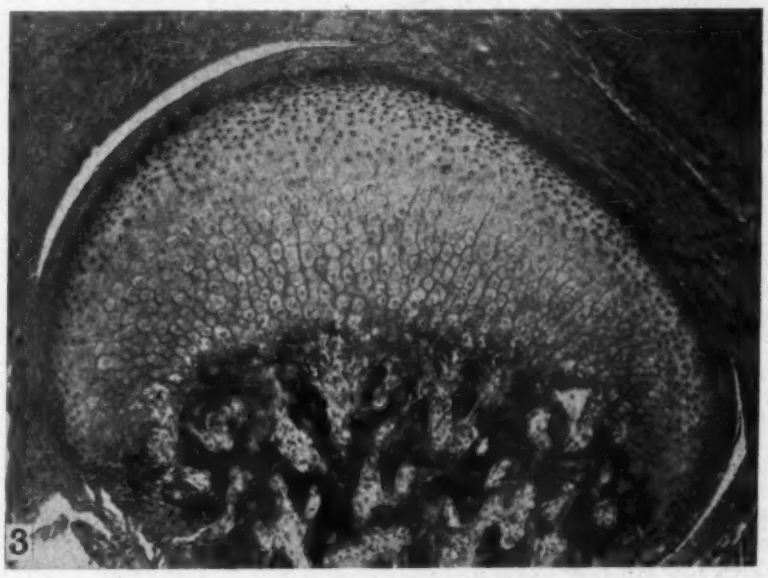

Fig. 3.—Maximum response to 39 days of growth hormone injections, begun after a postoperative interval of 349 days. (Age at operation, 27 days.) (Sp. 8776, Pl. 8542.)

sensitivity of these animals to this hormone. The response of the mandibular joint of hypophysectomized rats to thyroxin after an injection period of thirty-nine days is shown in Fig. 4. The dose of thyroxin used in this experiment produced only mild activity in the tissues of the articulation. Calcification of

the cartilage has decreased or disappeared. A sharp line of demarcation between the intermediate and embryonic zones has therefore disappeared. The slight increase in width of the cartilage may involve some increase in cell size. The amount of matrix is definitely increased. The dense bone of the ramus is almost identical with that of the control. There is no clear-cut increase in the size of number of vascular channels.

Injection of Growth Hormone With Thyroxin.—The combination of the two hormones was given to a group of 9 rats. The range of postoperative age

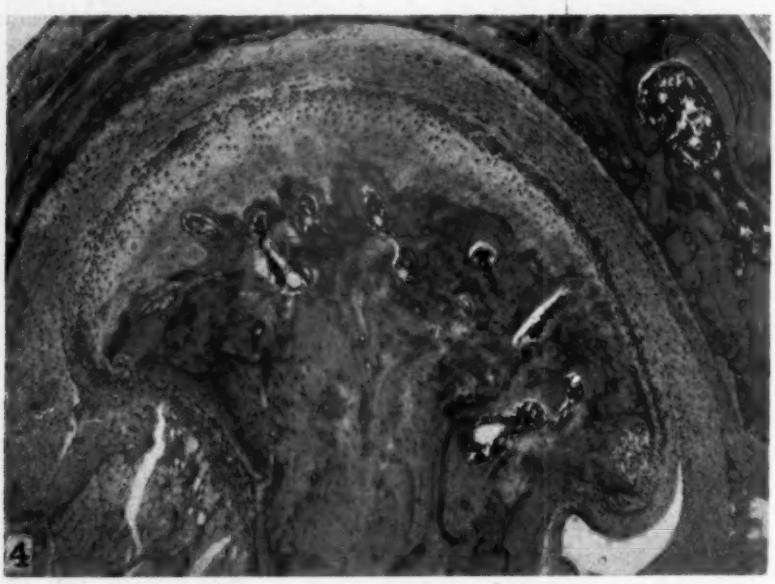

Fig. 4.—Response to 39 days of thyroxin injections, begun after a postoperative interval of 307 days. (Age at operation, 26 days.) (Sp. 8783, Pl. 8548.)

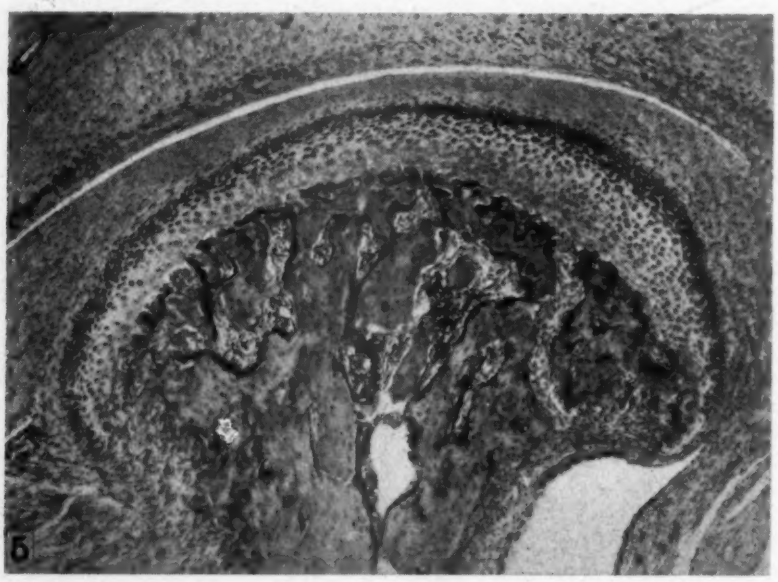

Fig. 5.—Response to 39 days of combined injections of growth hormone and thyroxin, begun after a postoperative interval of 377 days. (Age at operation, 27 days.) (Sp. 8792, Pl. 8553.)

at onset of injection was 285 to 433 days. The doses of growth hormone and thyroxin were the same as in the groups receiving these substances separately. The effect on the mandibular joint is shown in Fig. 5. A definite stimulation, somewhat similar to the minimum response to growth hormone alone is observed. Reactivation of the cartilage of the condyle, in the animal illustrated, as well as in all others of this group, is characterized by an increase in the number of cells and a decrease in intercellular matrix. The matrix of the cartilage is no longer calcified. Cell size is only slightly increased and no vacuolation is present. The dense bone of the condyle has been reopened by many vascular channels. Vascular loops and osteoblasts have gained access to the cartilage. The resorption of the bone of the ramus, and the amount of contact between marrow and cartilage attained here is not as extensive as in the group receiving growth hormone alone. The number of osteoblasts on the surface of the trabeculae is, however, very great. The stimulation present in the cartilage-like tissue of the fossa is similar to that observed in the group receiving growth hormone alone. There is an increase in the cellularity of the fibrous tissues of the articular surfaces.

SUMMARY AND CONCLUSIONS

From this investigation it may be concluded that growth processes in the senescent mandibular joints of hypophysectomized rats may be restored to juvenile vigor by administration of pituitary growth hormone.

Thyroxin as given in this experiment not only failed to reactivate growth at the mandibular joint, but when injected simultaneously with growth hormone inhibited the response to the growth hormone. This was in contrast with the finding[5] that thyroxin augmented the action of growth hormone on osteogenic processes at the proximal epiphyseal cartilage in the tibias of these animals. The response of the cartilage covering the head of the tibia was entirely comparable with that of the mandibular joint. Either the hormonal control of various points of growth must be different, or the amounts of these hormones necessary for facilitating osteogenic processes differ.

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THE EFFECTS OF A SINGLE MASSIVE DOSE OF VITAMIN D_2 (D-STOSS THERAPY) ON ORAL AND OTHER TISSUES OF YOUNG DOGS

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A DECADE ago European clinicians introduced the vitamin D-Stoss (shock) technique for the prevention of rickets in infants.[6] This treatment consisted of the administration of large single doses, of ½ million international units or more, of vitamin D. Since the introduction of this method, large single doses of vitamin D_2* or D_3† have been employed in this country also.[18, 22] Administration of as high as 1½ million international units daily to human beings as a treatment for refractory rickets has been tried.[1] Warnings have been expressed[2, 9, 10, 12, 13, 22] against too much enthusiasm in biologic therapy because of marked roentgenographic and histologic changes in dental and paradental structures of dogs as the result of overdoses of vitamin D. Complete knowledge on the storage and destruction of excessive amounts of vitamin D is not available as yet; studies along these lines have been conducted in experimental animals[8, 13] and in human beings.[14] Assay of the various body tissues of dogs, sacrificed three days after a large single dose, accounted for less than 10 per cent of the original massive dose.[11] Caution was advised against the acceptance of the vitamin D-Stoss therapy for rickets or its prevention until more is known about the possible damaging effects.

The hypercalcemia which results from hyperparathyroidism and that from the toxic effect of overdosage of vitamin D are of different physiologic origins.[16] The former is from a withdrawal of calcium from the body stores and the latter from an increased absorption from the intestines or diminished loss through the feces. Deposition of minerals in bone, dentine, and soft tissue has been observed following the hypercalcemic state of both hyperparathyroidism and hypervitaminosis D.[15] Pathologic calcifications have been demonstrated in dogs on the surfaces of bone trabeculae, and tooth roots; connective tissue, as for instance Sharpey's fibers, and pulp tissue showed amorphous highly calcified depositions.[2] Small malformed teeth were also observed in these animals.

The establishment of the maximum nontoxic dose of vitamin D is a difficult task, as various species and even individual animals of the same species differ in their tolerance of overdosage of vitamin D. In addition, the vitamin D products used by investigators have varied as to source and method of prepara-

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*D_2—Activated plant sterol (ergosterol).

†D_3—Activated animal sterol (7-dehydrocholesterol).

tion. In spite of the lack of information concerning the toxic effects of hypervitaminosis D, many clinicians continue to use massive doses for treatment of hay fever,[14] chronic arthritis,[4, 5, 7, 20, 21] psoriasis,[3] and other diseases. Severe reactions have been observed and it is possible that damage to body tissues occurs without the immediate appearance of symptoms.

Published reports indicate that there is a great variation in the effects of vitamin D overdosage on skeletal structures; some investigators have found "typical rickets"; others, osteodystrophia fibrosa; some, hypercalcification; and still others, no alterations. Comparison of results is rendered very difficult because of differences in species of animals and diets used, experimental arrangements, as well as dosages, sources, and preparation of the vitamin D. The present investigation was undertaken to study the effects of one single massive dose of vitamin D on bone, teeth, and other tissues.

EXPERIMENTAL MATERIAL

Seven purebred cocker spaniels were divided into control and experimental groups as shown in Table I. Group I consisted of two control dogs, 320 and 330 days of age, respectively, at autopsy (No. 250, 256), which received a purified diet.* These animals received normal amounts of vitamins A & D

TABLE I. DISTRIBUTION OF ANIMALS AND EXPERIMENTAL DATA

GROUP	DOG* NUMBER AND SEX	TREATMENT	AGE AT ADMINISTRATION OF VITAMIN D_2 (DAYS)	AGE AT AUTOPSY	REMARKS
I	(250) ♂	Control, purified diet. 72 I.U. vit. D/kg/day. Purified diet control	39	330	Vitamin A, 800 I.U./kg/day
	(256) ♂	Control, purified diet. 72 I.U. vit. D/kg/day. Purified diet control	39	320	Vitamin A, 10,000 I.U./kg/day
	(428) ♀	One dose of 450,000 I.U. irradiated ergosterol	34	71	Stock diet. Dying 37 days after overdose, sacrificed
	(433) ♂	One dose of 450,000 I.U. irradiated ergosterol	29	117	Stock diet. Was sacrificed 88 days after overdose
II	(432) ♂	One dose of 450,000 I.U. irradiated ergosterol	29	270	Stock diet. Sacrificed 271 days after overdose
	(431) ♂	One dose of 450,000 I.U. irradiated ergosterol	29	270	Stock diet. Sacrificed 271 days after overdose
	(427) ♂	One dose of 450,000 I.U. irradiated ergosterol	34	272	Stock diet. Sacrificed 238 days after overdose

*Refers to the official records of the Department of Home Economics, University of California, Berkeley, California.

*Purified diet: 45.8 per cent washed casein, 20.3 per cent cornstarch, 20.0 per cent granulated sugar, 10.0 per cent hydrogenated cottonseed oil, 2.4 per cent salt mix, 1.5 per cent calcium carbonate. Vitamin supplements are fed as follows per kilogram per day: Thiamine hydrochloride 100 gamma, pyridoxine 100 gamma, riboflavin 100 gamma, nicotinic acid amide 2 mg., calcium pantothenate 3 mg., para-aminobenzoic acid 3 mg., choline 5 mg., vitamin D 100 I.U., vitamin A 800 I.U., wheat germ oil 1 Gm.; inositol 25 mg. per 100 grams of diet. A 2,050-Gm. batch of salt mix contains: KH_2PO_4 205.5 Gm., $CaH_4(PO_4)_2$ 563.2 Gm., $MgSo_4$ 49.5 Gm., NaCl 224.4 Gm., Fe citrate 22.0 Gm., Ca lactate 986.7 Gm., NaF 0.682 Gm., KI 0.005 Gm., $MnSO_4$ 0.2167 Gm., $K_2Al_2(SO_4)_4$ 0.006 Gm.

and were at no time exposed to the effects of hypervitaminosis D. Group II consisted of five dogs (Nos. 428, 433, 432, 431, 427) which were placed on the same purified diet and received one massive dose of 450,000 I.U. of vitamin D_2 when 29 days of age (Dogs 433, 432, 431) or 34 days (Dogs 428 and 427). At autopsy they were between 71 and 272 days old (Table I).* The jaws were immediately fixed in 10 per cent neutral formol. After being roentgenographed they were decalcified in an aqueous solution of 5 per cent nitric acid, embedded in nitrocellulose, sectioned, stained with hematoxylin and eosin, and studied histologically.

RESULTS

Roentgenographic Aspect.—Roentgenograms of the right lower jaws of control and experimental animals are reproduced in Figs. 1, 2, and 3.

The control dogs showed well-developed jaws with large teeth. Fig. 1 shows that the roots are straight and are without any distortions or deformities. The distribution of the cortical and trabecular bone is even and dense. The pulp canals and chambers are free of pulp stones; the alignment of the teeth is regular and no malposition is evident.

The roentgenographic changes resulting from the administration of a single massive dose of vitamin D_2, are shown in Figs. 2 and 3. Even though the deciduous teeth of the younger experimental dog (No. 428) do not show any deviation from normal, partially formed permanent teeth do contain large pulp stones. The pathologic effects of a single massive dose of vitamin D_2 in the older animals are demonstrated in Fig. 3. Large calcified areas are observed in the pulp chambers. The character and quality of the supporting bone is altered, and while distortion and resorption of the roots are marked, they follow no characteristic pattern. There is no marginal alveolar atrophy although the bone structure appears porotic. The absence of pulp stones in the second and third molars of all experimental dogs indicates that the pathologic changes occurred before the formation of these teeth had started.

Histologic Aspect.—The photomicrograph of a central section through the last premolar of the *control* dog No. 250 is seen in Fig. 4. The tooth is large and the roots are straight. The marrow cavities are of even size with a regular distribution of coarse bone trabeculae. A normal balance between apposition and resorption is seen. The periodontal membrane space of the premolars averages 170 micra in width. The blood supply is plentiful, including an abundance of large capillaries throughout the paradental tissues.

The five experimental dogs were divided into two sections according to the length of the recovery period, i.e., the number of days between the administration of vitamin D and autopsy.

Short Recovery Period (37 and 88 days).—The effects of a massive dose of vitamin D on dental and paradental structures during the developmental period as observed in Dogs 428 and 433 (Table I) were as follows:

1. In the early formative stage, before the roots or the bifurcation had begun to develop, the first molar shows a large pathologic calcification (*Y*) filling

*Chemical analyses of blood serum, changes in general behavior and appearance of these animals, and complete necropsy findings are included in a separate report.

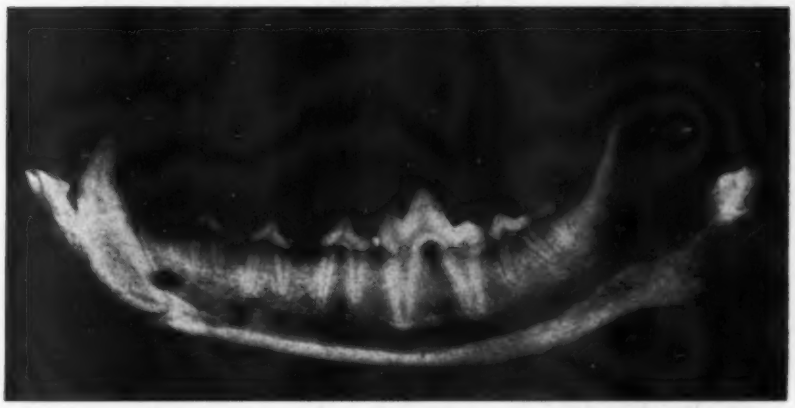

Fig. 1.—Reproduction (natural size) of the roentgenogram of a purified-diet control dog, No. 250, 330 days of age at autopsy. Rtg. 900, Pl. 1971.)

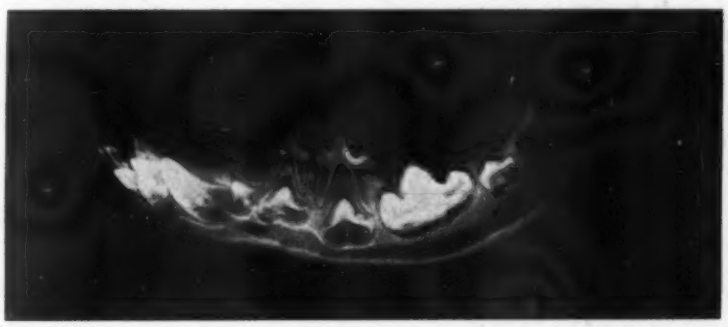

Fig. 2.—Reproduction (natural size) of the roentgenogram of Dog 428, which received a single massive dose of vitamin D_2 at 34 days of age, autopsied at 71 days of age. (Rtg. 775, Pl. 7780.)

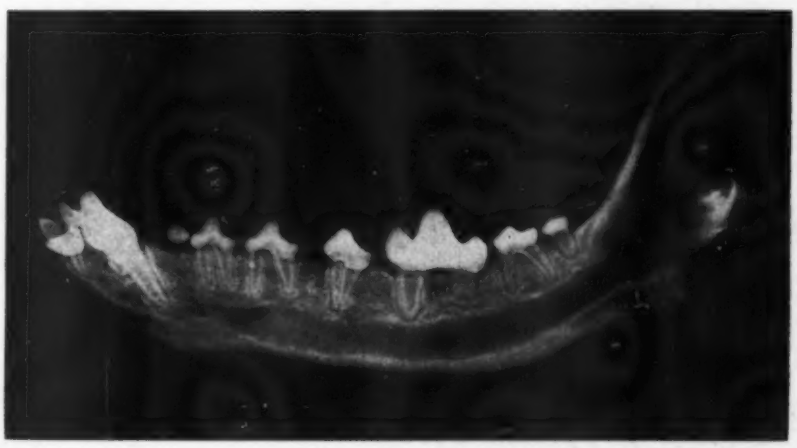

Fig. 3.—Reproduction (natural size) of the roentgenogram of Dog 432 which received a single massive dose of vitamin D_2 at 29 days of age, autopsied at 270 days of age. (Rtg. 782, Pl. 1986.)

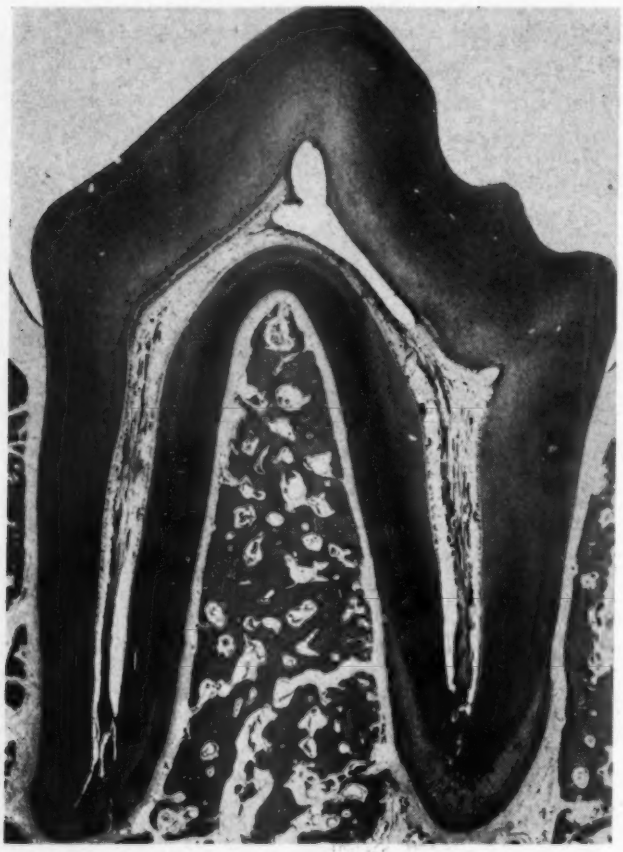

Fig. 4.—Photomicrograph of a central section through the last premolar of purified diet control dog No. 250. (Spec. 1522, Pl. 6803.) (×10.)

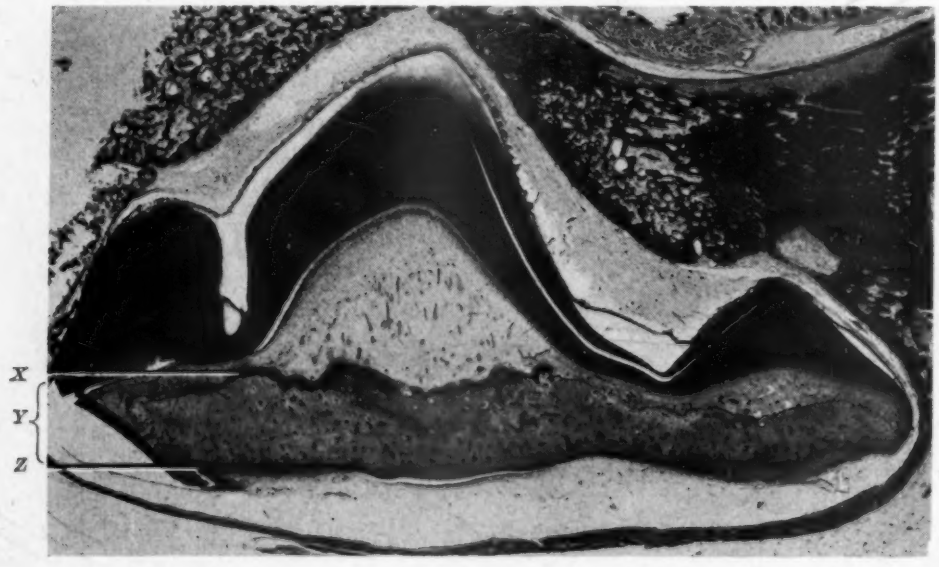

Fig. 5.—Photomicrograph of a central section through the developing permanent first molar of Dog 428 which received a single massive dose of vitamin D_2 at 34 days of age, autopsied 37 days later at 71 days of age. Note pathologic calcification occupying nearly the entire width of the pulp chamber. (Spec. 4669, Pl. 954.) (×10.)

half of the pulp chamber (Fig. 5). Dentinoid tissue bordered by a distinct line of odontoblasts is beginning to form and to encase this pathologic area. Immediately surrounding the blood vessels, a darker staining reaction is observed, indicating the highly calcified nature of this tissue. Even though roentgenographically these areas appear as pulp stones, histologically they are identified as amorphous pathologic calcifications. They are referred to as pulp stones throughout this report because of the roentgenographic appearance.

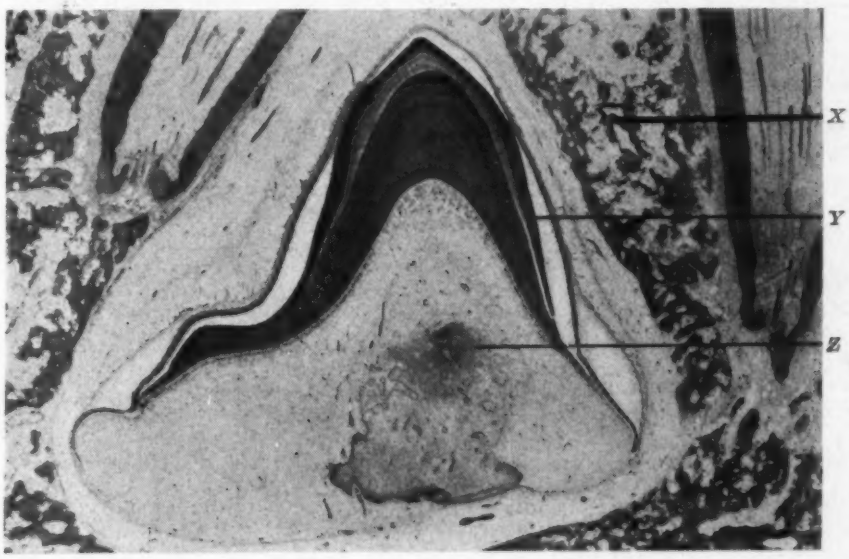

Fig. 6.—High magnification of developing permanent premolars of Dog 428 (same as Fig. 5). Note pathologic calcification in enamel organ (*Z*) and around trabeculae (*Y*) and increased calcification of outer layers of the enamel (*X*). (Spec. 4670, Pl. 1992.) (×15.)

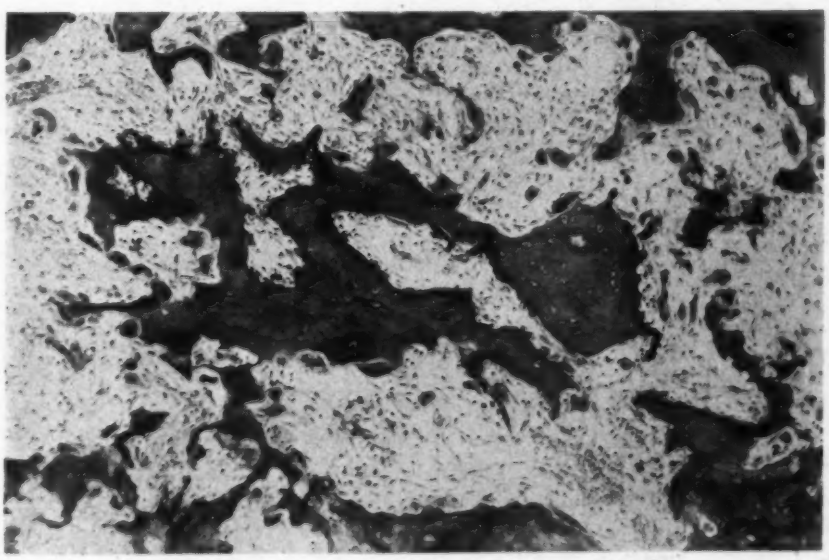

Fig. 7.—Higher magnification of *Y*, Fig. 6, showing pathologic calcification around the trabeculae. (Spec. 4670, Pl. 955.) (×200.)

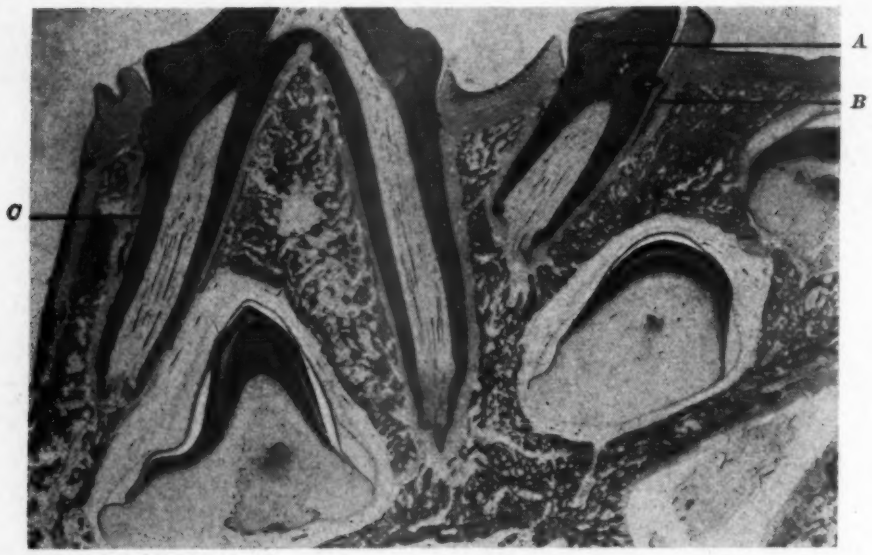

Fig. 8.—Photomicrograph of a central section through the developing permanent premolars and deciduous molars of Dog 428 (same as Fig. 5). Note pathologic calcification around the roots and in the periodontal membrane of the deciduous teeth at *B* and *C*; also odontodystrophy at *A*. Beginning pathologic calcification of developing permanent tooth may be seen. (Spec. 4670, Pl. 956.) (×10.)

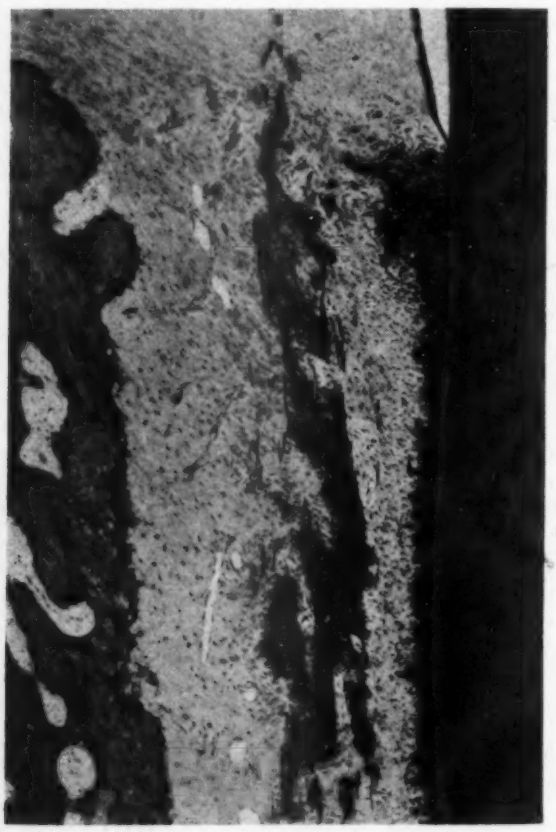

Fig. 9.—High magnification of *B* in Fig. 8, showing pathologic calcification in periodontal membrane and of the cementum of a deciduous tooth. (Spec. 4670, Pl. 1996.) (×130.)

2. In the premolar area the surfaces of the bone trabeculae show a darker staining as seen at *Y* in Fig. 6. In a magnification of one area (Fig. 7) numerous osteoclasts are observed, indicating that the resorptive process of bone over the erupting permanent premolar is very active. These dark-staining areas are highly calcified amorphous deposits with a large number of entrapped cells.

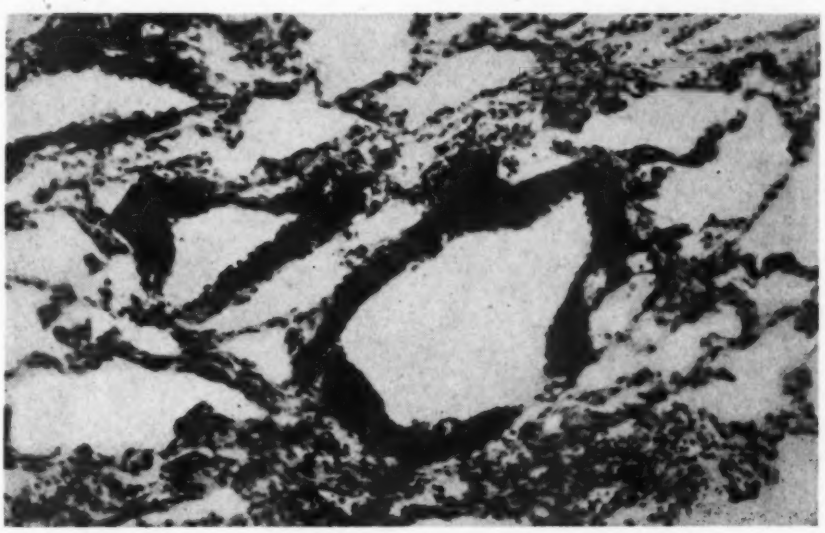

Fig. 10.—High magnification of a histologic section of the lungs of Dog 428 (same as Fig. 5). Note deposition of calcium in the walls of the alveoli. (Spec. 4671, Pl. 8235.)

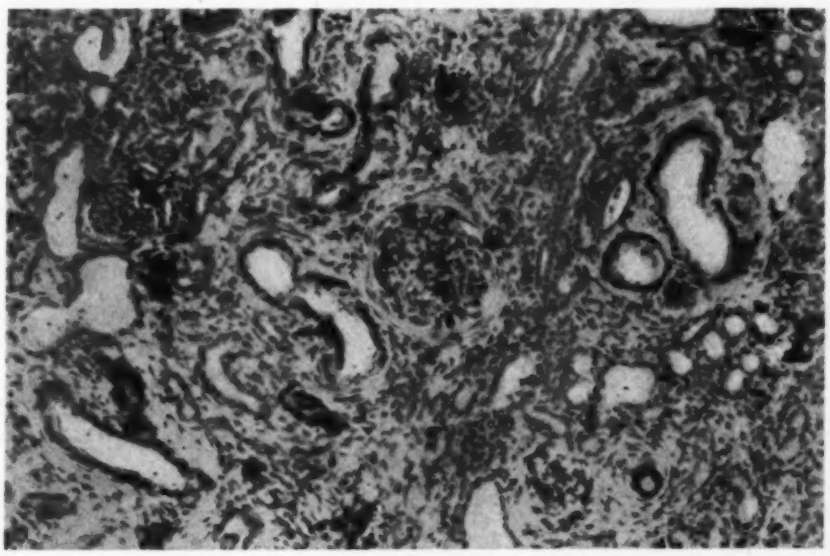

Fig. 11.—High magnification of a histologic section of the kidney of Dog 428 (same as Fig. 5). Note calcium deposition in the glomeruli and large blood vessels. (Spec. 4671a, Pl. 8234.)

3. The outer half of the enamel of the first premolar (Fig. 6, Y) is more strongly basophilic than the inner portion, suggesting a great degree of calcification.

4. A large number of pathologic calcifications are found on the surface of the roots, the walls of the pulp canals of the deciduous teeth (Fig. 8, C), and fre-

quently in the periodontal membrane. Sometimes they are detached from the root surface as seen in a higher magnification (Fig. 9). Here the finest capillaries are filled with the same calcium-rich material. In other areas perivascular infiltration or deposition is distinct.

5. Interference with dentinogenesis, as seen in Fig. 8 at *A*, in the deciduous teeth after the onset of the hypercalcemia is indicated by a definite striation.

6. In the deciduous teeth pathologic calcifications in the pulp tissue are absent.

7. There is no suggestion that the activity of Hertwig's sheath is affected.

8. Histologic examination of the liver revealed no abnormal changes; however, calcifications are observed in the lungs (Fig. 10) and kidneys (Fig. 11) of Dog 428 only (this dog lived 37 days after the single overdosage of vitamin D_2). The sites of deposition in the kidney were primarily in the glomeruli and walls of the larger blood vessels. In the lungs the respiratory bronchioles were calcified. This confirms the findings in a fatal case due to vitamin D intoxication.[24]

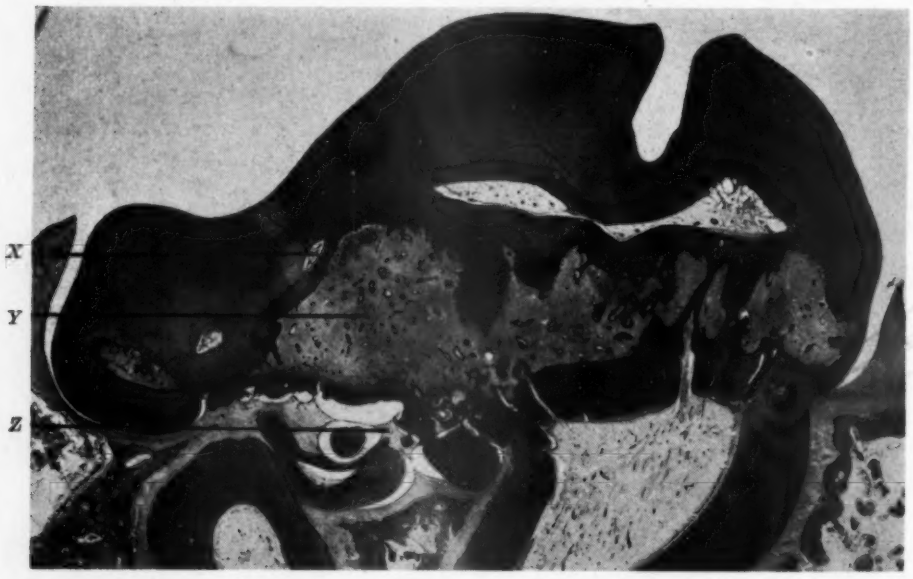

Fig. 12.—Photomicrograph of a central section through the first molar of Dog 431 which received a single massive dose of vitamin D_2 at 29 days of age, age at autopsy 280 days. Note nearly complete pathologic calcification of the pulp chamber (*X* and *Y*). Compare with calcification in Fig. 5. Distorted roots, a typical dentine and enamel formation in the bifurcation of its roots are seen at *Z*. (Spec. 4682, Pl. 8135.) (×15.)

Long Recovery Period (238 and 241 days).—The dogs (Nos. 432, 431, 427) which lived for a longer period after the massive dose of vitamin D showed effects similar in many respects to those just described.

1. Pathologic calcifications almost completely occupy the pulp chamber (Fig. 12). Perivascular calcification has advanced to the stage that the blood vessels are enveloped and in some instances the walls are entirely calcified as seen in Fig. 13.

2. Degeneration of most odontoblasts is observed in the pulp chambers (Fig. 12); however, a few are seen in typical arrangement in the horns of the chambers under the cusps and in the pulp canals.

3. The dentine which encases the pathologic calcification is often seen connecting with the dentin of the wall of the pulp chamber and in some areas the enclosed soft tissue is necrotic (Fig. 12, *X*).

4. At the bifurcation of the roots, communication between the paradental tissues and the pulp chamber is seen. Frequently aberrant enamel formation can be noted in these areas (Fig. 10, *Z*).

5. The roots are severely malformed.

6. The gingivae are normal in appearance without inflammation or marginal bone atrophy.

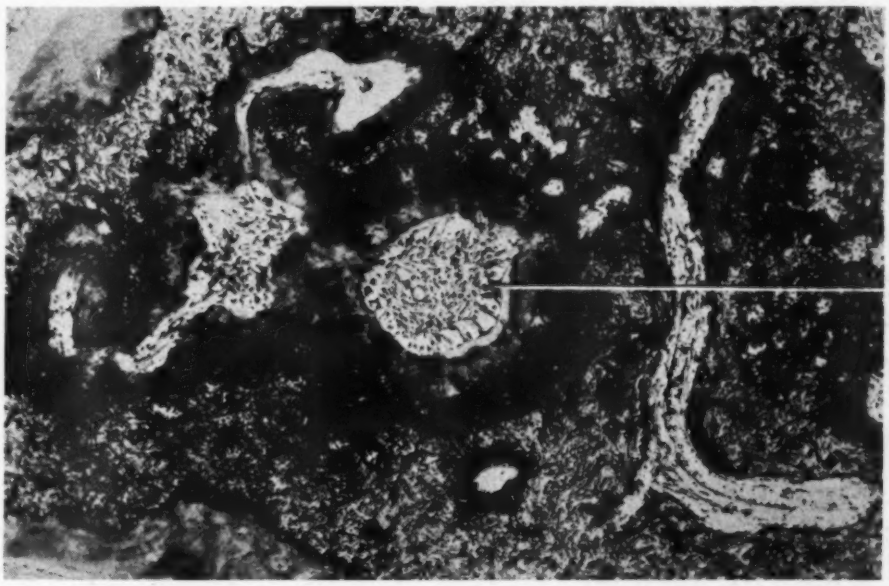

Fig. 13.—High magnification of *Y*, Fig. 11, showing calcification within the pulp chamber. Note perivascular calcification and necrosis of enclosed tissue (*X*). (Spec. 4682, Pl. 1987.) (×130.)

SUMMARY AND CONCLUSIONS

The purpose of this study was to investigate the effects of a single massive dose of 450,000 I. U. of vitamin D_2, administered to five purebred cocker spaniels at approximately 1 month of age. The osteoporosis of the mandible and the deformation of the teeth observed in the roentgenograms were confirmed histologically. The pathologic calcifications have the same appearance in the dogs with short recovery periods as in those with the long recovery periods. The dogs with recovery periods of approximately eight months showed severely deformed roots. Apparently Hertwig's sheath is very resistant to the toxic effects of hypervitaminosis D_2, since root formation continued. The normal appearance of the second and third molars of the dogs with long recovery periods is perhaps due to the fact that the teeth calcify some time after the age at which the overdosage was administered (approximately 30 days). The deciduous teeth, only present in the dogs with short recovery periods, show no evidence of pathologic calcification in the pulp tissue. Pathologic calcifications were observed in the lungs and kidneys of the dog with the shortest recovery period,

but not in the liver. Calcification was not observed in these organs of the other dogs in this study.

The severe pathologic changes observed in the bones, teeth, lungs, and kidneys of dogs following a single massive dose of vitamin D_2 provide evidence that the previous warnings regarding the dangers of administering chronic excessive doses of vitamin D must be extended to cover the changes following the administration of a single massive dose. Until the maximum tolerance doses are established, the administration of excessive amounts of vitamin D_2 or D_3 must be made with caution and cognizance of the possible deleterious effects.

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CHANGES IN ORAL STRUCTURES OF THE DOG PERSISTING AFTER CHRONIC OVERDOSES OF VITAMIN D

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THE major etiological factors of rickets have been found to be disturbances of calcium and phosphorus metabolism and lack of vitamin D. The composition of the diet as to calcium-phosphorus ratio and acid-base balance is of such importance that unless correct proportions and amounts of these and other factors are controlled, vitamin D in any dose will have little effect in the prevention or cure of rickets.[4, 7, 12, 23] Vitamin D has been shown to influence the composition of tissue fluids so as to allow the minerals to be deposited normally in growing bone. This biologic effect of vitamin D has been used as the method of assay of the various forms and sources of antirachitic substances. In 1927, shortly after the discovery of the high antirachitic potencies of irradiated foods[9, 25] and irradiated ergosterol,[28] the administration of large amounts of concentrated sterols was found to result in severe cachexia in rabbits[18, 19] and pathologic changes in rats.[24]

Large doses of vitamin D_3* produce damaging results more rapidly in rats than D_2;† however, symptomatic recovery from the toxic effects‡ is more rapid after the removal of the excess dose of D_3 and D_2.[17] The difference in the effects of large doses of D_3 and D_2 is due to the more rapid excretion of the former.[15] D_2 also produces a hypercalcemia of longer duration than do comparable amounts of D_3. The hypercalcemia resulting from overdoses of vitamin D is due to an increased intestinal absorption or diminished fecal loss of calcium. During the fall of the calcium level following the hypercalcemic state, there is a deposition of calcium in bone, dentine, and soft tissues.[22]

The toxic effects as a result of large doses of vitamin D have been repeatedly demonstrated.[2, 3, 5, 6, 8, 10, 11, 12, 15, 20, 21, 22, 26, 27, 29] In rats, chronic hypervitaminosis D inhibits normal calcification of bones, resulting in histologic changes similar to those in rickets. In teeth, alternating normal and excessively calcified layers of dentine are formed, corresponding to the hypercalcemic state and the recession of the blood calcium level. However, no alterations were found in the calcification rhythm of dentine or rate of eruption.

From the Division of Dental Medicine, College of Dentistry, the George Williams Hooper Foundation for Medical Research, and the Department of Home Economics, University of California, San Francisco and Berkeley, California.

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*D_3—Activated animal sterol (delsterol).

†D_2—Activated plant sterol (ergosterol).

‡The clinical symptoms of hypervitaminosis D generally recognized are anorexia, nausea, cachexia, lassitude, psychosis, polydypsia, polyuria, diarrhea, and hyperglycemia.

In dogs, areas of amorphous highly calcified substances have been demonstrated on the surface of bone trabeculae and in diminished marrow cavities.[2, 3] Additional calcification of Sharpey's fibers occurred. Teeth were smaller and malformed with multiple pulp stones. Regarding these pulp stones, it was stated that "there appears little doubt that the excess of irradiated ergosterol is primarily responsible for them in these animals."[2] It has been pointed out that in dogs excessive vitamin A intake may decrease the harmful effect of overdosage of vitamin D.[13-17]

The toxicity of vitamin D overdose in human beings has been again demonstrated recently[1] by the autopsy findings of hypercalcification of viscera and hard tissues.

In general, there is a great variation in the effects of vitamin D overdose in that some investigators have found typical rickets, others osteodystrophia fibrosa, or osteosclerosis and pathologic calcification, whereas others have found no alterations of osseous structures. *Such variables as difference in species of animals, diet, design of experiment, source, treatment, and dose of the vitamin D product contribute greatly to the differences in pathologic effects reported.*

The following roentgenographic and histologic studies were made of the mandibular structures of dogs which received continued overdoses of vitamin D for extended periods of time, to determine whether the pathologic changes would persist during a succeeding recovery period.

EXPERIMENTAL MATERIAL

Four purebred cocker spaniels received a purified diet (Table I).* Two were control dogs (Nos. 256, 250) autopsied at 320 and 330 days of age. The two experimental dogs (Nos. 264, 266) were fed excessive daily doses of vitamin D over long periods of time beginning at 60 days of age. The vitamin D was withdrawn intermittently because of the severe general toxic effects.

Dog 264 received 10,000 I.U. vitamin D_3 (Du Pont) and 10,000 I.U. vitamin A per kilogram of body weight per day for 127 days. A total of 1,270,000 I.U. vitamin D_3 was administered and the dog was sacrificed at 386 days of age. The vitamin D_3 and A were given as follows:

60 days of age, started on hypervitaminosis D_3 and A
18 days on hypervitaminosis
41 days off hypervitaminosis
59 days on hypervitaminosis
12 days off hypervitaminosis
50 days on hypervitaminosis
146 days recovery period

Dog 266 received vitamin D_2 for a period of 145 days, intermittently, as follows:

60 days of age, started on hypervitaminosis D_2 and A
24 days on hypervitaminosis
45 days off hypervitaminosis
121 days on hypervitaminosis
146 days recovery period

*Composition of this purified diet is given elsewhere.[3]

TABLE I. EXPERIMENTAL DATA

GROUP	DOG NUMBER AND SEX	TREATMENT	AGE AT BEGINNING OF EXPERIMENT (DAYS)	PERIOD ON EXP. DIET (DAYS)	RECOVERY PERIOD (DAYS)	AGE AT AUTOPSY (DAYS)
I	256 ♂	Purified diet control	39	281		320
	250 ♂		39	291		330
II	264 ♂	10,000 I.U./kg./daily of Vit. D_3 and 10,000 I.U./kg./daily Vit. A	60	127 Intermittently	146	386
	266 ♂	10,000 I.U./kg./daily of Vit. D_2 and 10,000 I.U./kg./daily Vit. A	60	145 Intermittently	146	396

This dog received a total of 1,450,000 I.U. vitamin D_2 and was sacrificed at 396 days of age. After autopsy the jaws of all dogs were roentgenographed, fixed in 10 per cent neutral formol, decalcified, and embedded in nitrocellulose. Sections were stained with hematoxylin and eosin.

RESULTS

1. *Roentgenographic Aspect.*—

Group I: The control dogs show well-developed jaws, large teeth, and straight roots without any distortion or deformities (Fig. 1, *A*). The distribution of the bone trabeculae is uniform. The pulp canals and chambers are free of pulp stones; the alignment of the teeth is regular and no malposition is evident.

Group II: The jaws of the treated dogs do not appear to be stunted in length (Fig. 1, *B* and *C*); however, the vertical dimension and the quality of the osseous and dental structures is inferior to that of the purified diet controls. Several pulp stones can be noted in the teeth of Dog 264 (Fig. 1, *B*). Distortion of the roots is marked in Dog 266 (Fig. 1, *C*). There is a generalized marginal horizontal and vertical atrophy in both dogs; however, this appears more advanced in the dog given vitamin D_3 (Fig. 1, *B*). The roentgenograms show irregular distribution of coarse bone trabeculae with large marrow spaces in the lower portions of the mandible.

2. *Histologic Aspect.*—

Group I: The teeth appear large with straight roots (Fig. 2, *A*). The marrow cavities are of even size with a regular distribution of coarse bone trabeculae. The periodontal membrane space averages 170 micra for the premolars. Normal osteogenesis is evidenced by a balance in the number of osteoclasts and osteoblasts. The blood supply is plentiful, including an abundance of large capillaries throughout the paradentium.

Group II: After the recovery period the following outstanding pathologic changes persist:

1. Irregular distribution of bone trabeculae is evident (Fig. 2, *B*). Numerous interruptions of the alveolar bone are occupied by blood vessels and marrow tissue. In some areas the marrow elements are replaced by fat. Marginal horizontal atrophy has involved the bifurcation with the development of granulation tissue (Fig. 2, *B*, *x*). Round-cell infiltration reaches deep into the marrow cavities.

2. A thick layer of cementum is covering the entire root surface. It differs distinctly from that observed in the normal control. A magnification of the apical third of the mesial root of the third premolar is shown in Fig. 3. The original root surface (Fig. 3, *a*) is very irregular in outline. Adjacent to the fine line of primary cementum several areas of pathologic calcifications can be noted (Fig. 3, b). In some places these correspond to changes observed in dogs on chronic hypervitaminosis D without a recovery period.[2] Elsewhere they are light-staining calcified layers of varying contour (Fig. 3, *c*) which appear similar in structure to the darker-staining outer layer bordering the periodontal membrane (Fig. 3, *d*). The cementoblasts are so numerous as to constitute an almost continuous line (Fig. 3, *e*).

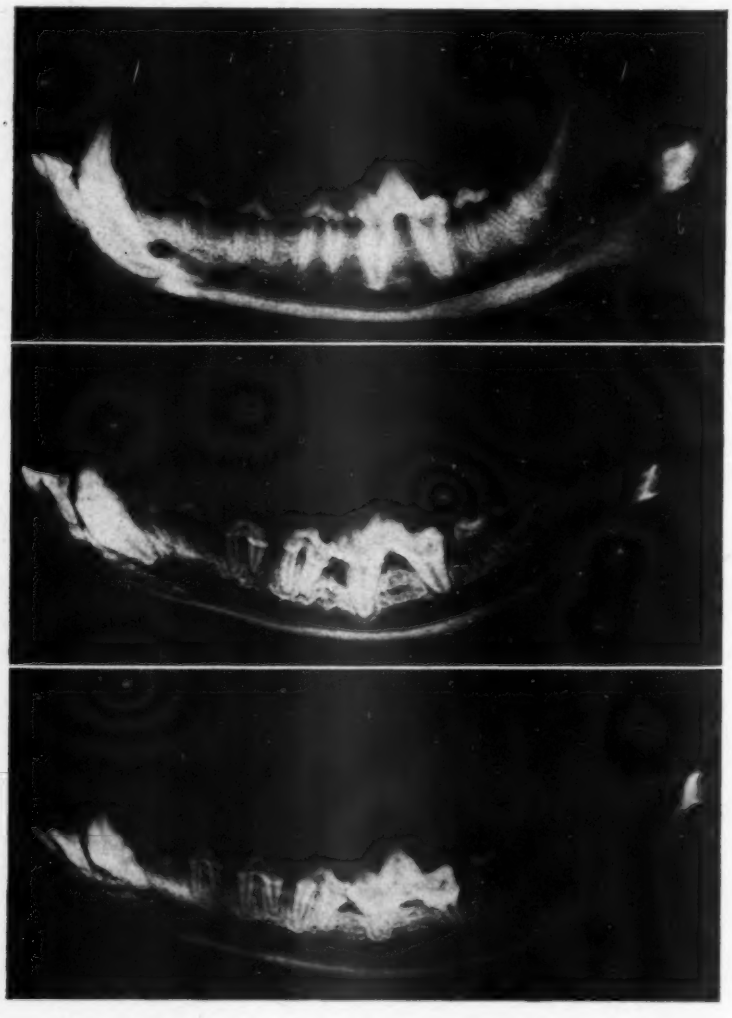
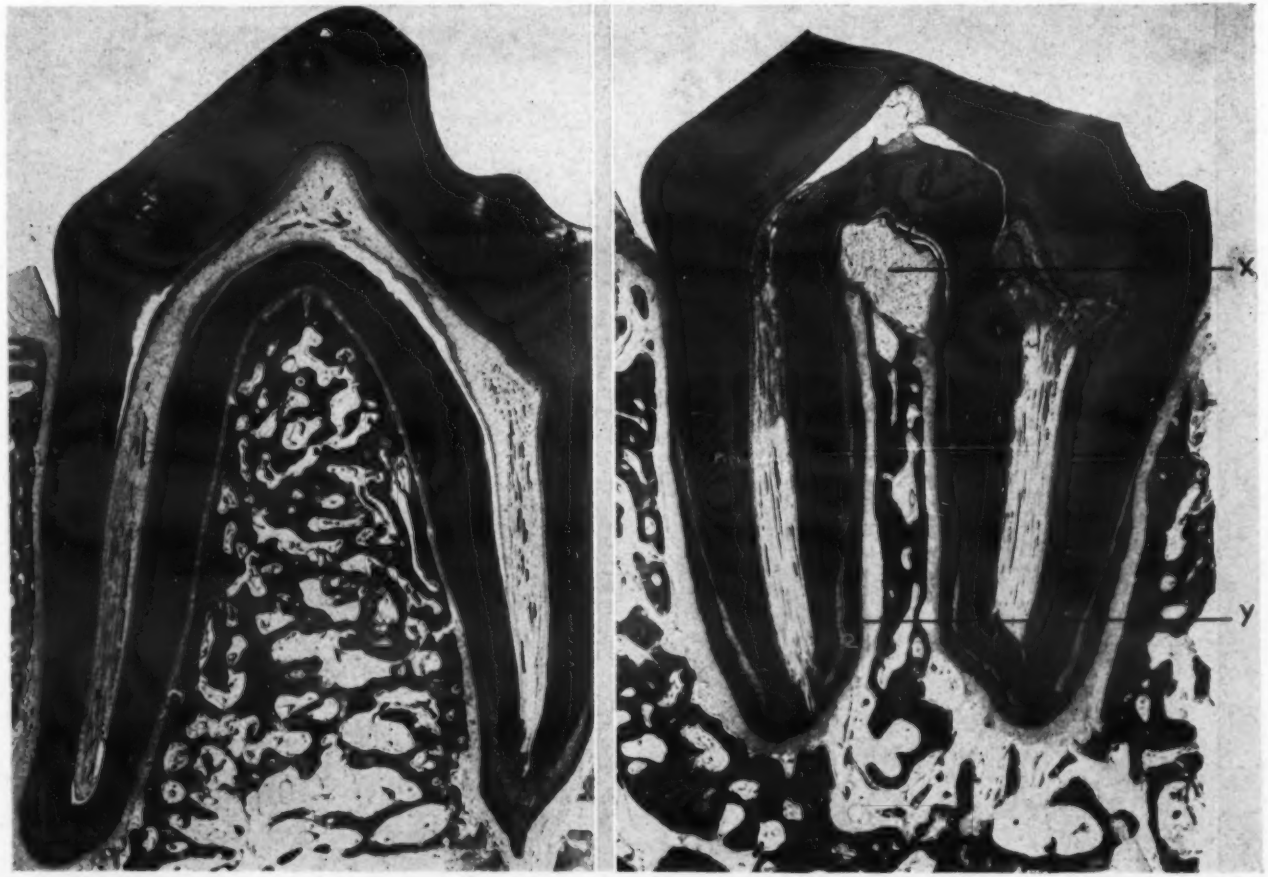


Fig. 1.—*A*, Dog 250: Purified diet control; 330 days of age at autopsy. Roentgenogram (natural size) of right lower jaw. (R-gram No. 900, Pl. 1971.)

B, Dog 264: Administration of chronic excessive doses of vitamin D_2 beginning at 60 days of age for 127 days intermittently. A recovery period of 146 days was allowed before autopsy at 386 days of age. (R-gram No. 1114, Pl. 1972.)

C, Dog 266: Administration of chronic excessive doses of vitamin D_2 beginning at 60 days of age for 145 days intermittently. A recovery period of 146 days was allowed before autopsy at 396 days of age. (R-gram No. 1114, Pl. 1973.)



A. *B.*

Fig. 2.—*A*, Dog 256: Purified diet control; 320 days of age at autopsy. Section through the third premolar (Spec. 4531, Pl. 6640).

B, Dog 264: Section through the third premolar. Note pathologic cementum formation on the surfaces of both roots (*y*); horizontal atrophy at the bifurcation and granulation tissue formation at *x* (Spec. 4547, Pl. 1988).

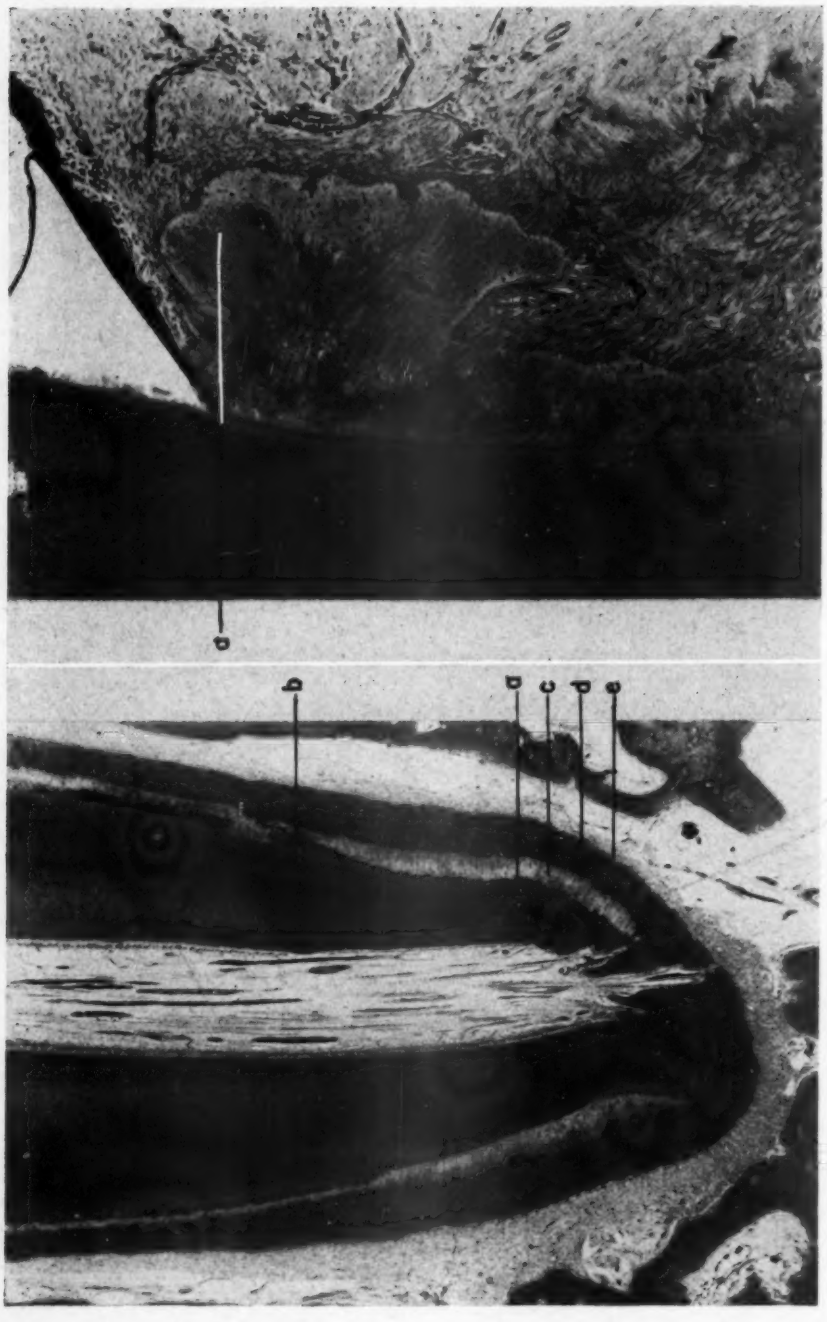


Fig. 3.

Fig. 4.

Fig. 3.—Magnification of apical third of mesial root in Fig. 2*B* (Spec. 4547, Pl. 7181).

Fig. 4.—Dog 264: *A*, Note pathologic calcification of connective tissue and periodontal membrane (Spec. 4547, Pl. 1990).

3. In the marginal area the same extensive cementum formation is found. At the level of the cementoenamel junction a thin layer of primary cementum covers the dentine surface (Fig. 4, *a*). External to the thin cementum layer there lies a broad, irregular mass of partially calcified fibrotic tissue, with a sharp border of fusiform cells forming a line of demarcation. The loose subepithelial connective tissue occupies the remainder of the gingival papillae. The stratified squamous epithelium on the surface of the soft tissue is markedly basophilic.

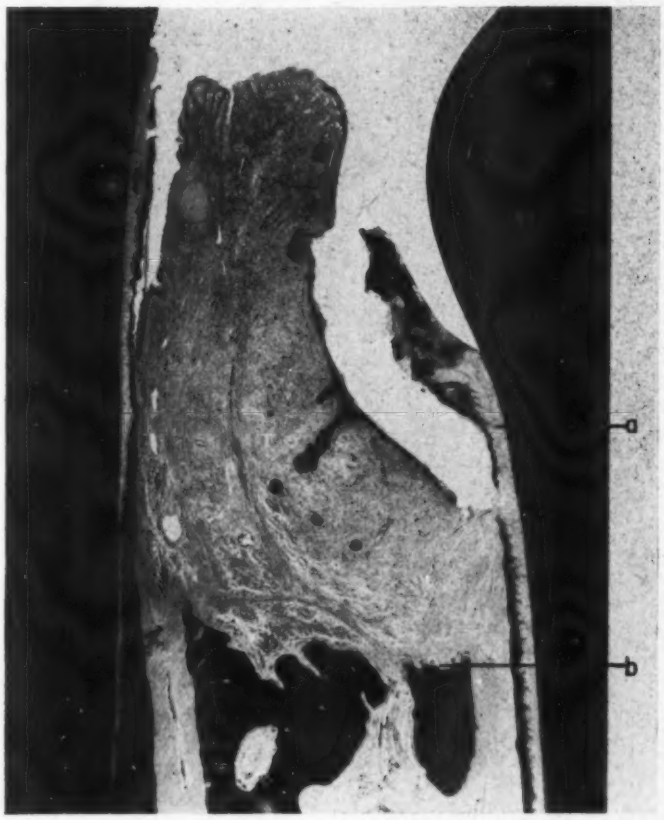


Fig. 5.—Dog 264: Note alveolar atrophy (*b*). Cementum spur is covering a portion of the cervical third of the enamel (*a*). Note osteoclastic activity (*b*) (Spec. 4547, Pl. 1993).

The interdental space from another area in the same dog is seen in Fig. 5. At *a* the original cementum with its characteristic light-staining reaction bears an irregular surface of intensely basophilic tissue within which calcium has been deposited. The interdental soft structures consist of dense fibrous tissue. Extensive granulation tissue has been formed. Large spurs of cementum-like structure extend over the cervical third of the enamel. The mesial surface of the third premolar shows deepening of the paradental pocket which has exposed the large cementum spur to the oral cavity. The remaining gingival tissue adjacent to the spur is severely irritated by the jagged projection. The gingival epithelium has proliferated through the interdental papilla with pearl

formation and fingerlike projections of epithelium reaching toward the alveolar bone. The alveolar margin is undergoing resorption and many osteoclasts are seen at Fig. 5, *b*.

Cementum formation has proceeded even farther toward complete calcification of the periodontal membrane fibers in a tooth formed earlier, such as the first molar shown in labiolingual section in Fig. 6. Cementum spurs have also reached in to the gingival papillae (Fig. 6, *b*).

Fig. 6.—Dog 264: Labiolingual section through the first molar. Note amorphous depositions in the center of the pulp chamber (*a*). Pathologic calcifications (*b*) may be observed also in the periodontal membrane forming an ankylosis with the alveolar bone. (Spec. 4548, Pl. 8125.)

4. Pulp stone formation is demonstrated in the labiolingual section of the first molar in Fig. 6. The crown portion of the pulp has been completely replaced by secondary dentin (Fig. 6, *b*) and amorphous calcifications (Fig. 6, *c*).

SUMMARY

Young dogs receiving daily excessive doses of vitamin D_2 and D_3 for a five-month period manifested profound pathologic changes, which included distorted and deformed roots, pathologic calcifications of connective tissues of the paradentium, hypercementosis, pulp stone formation, and advanced paradentosis. The changes persisted following a recovery period of similar duration. No evidence of healing or repair could be demonstrated. The warnings of other in-

vestigators regarding the danger of administering chronic excessive doses of vitamin D are further emphasized.

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THE HORMONES OF THE ANTERIOR PITUITARY

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EXPERIMENTAL biology has established the fact that the anterior lobe of the pituitary gland or hypophysis secretes six different substances into the blood stream.

There are two methods of investigating the secretion of any endocrine or internally secreting gland:

1. To convey abnormally large amounts of the secretion or secretions to normal animals and observe the effects. This could be called the method of overconveyal, and when these secretions have not yet been purified, the method of overconveyal has to be carried out by merely grinding up the fresh glandular material and putting a suspension of it, or crude extract of it, under the skin or between the muscles.

2. The other method is to remove surgically the gland whose internal secretions one is studying and to observe the effects of this removal.

Both methods of study have been used during the last twenty, and especially during the last ten, years to discover the function of the anterior hypophysis.

In 1921 Evans and Long put crude extracts of fresh bovine anterior lobe tissue by needle into the body cavity of rats. They used litter-mate brother and sister rats for controls and made intraperitoneal injections once daily for over a year. Within a few weeks it was apparent that the injected rats were growing at a faster rate than their normal sisters and brothers. In this way giants were for the first time experimentally produced. Shortly after this, P. E. Smith in the same laboratory successfully cut the pituitary gland out of young rats and found that they did not grow; but when he gave the same extracts employed by Evans and Long to make normal rats grow, he reestablished the growth of the hypophysectomized rats. It was assumed that this was because the anterior pituitary contained a growth stimulant or hormone.*

A few years later, Zondek in Germany and Smith in this country showed that another internal secretion or hormone must be secreted by the anterior pituitary—a hormone which causes the development and active function of the sex glands or gonads, so that it was called the gonadotrophic hormone. Zondek and Smith did this by merely inserting little pieces of fresh anterior pituitary tissues under the skin of immature rats and mice. Within three, or

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*There ensued many years of controversy as to whether the growth effects were due to a peculiar and separate substance which we would therefore have the right to name the growth hormone. It was held for example that some of the other hormones known to exist in anterior pituitary extracts could have brought about the superior growth. It is only in the last year or two that the growth hormone has been completely purified and characterized as a pure protein as completely as is the case with any other hormone in this organ.

four days at the longest, these baby rodents became sexually mature—an event which would have required a little over a month's time normally. I may remind you that a similar phenomenon is the basis of the now well-recognized earliest reliable test for pregnancy, the Aschheim-Zondek test. This is because another gonadotrophic substance, chorionic gonadotropin, is secreted by the membranes of the freshly implanted ovum into the mother's blood stream, whereupon it passes out into her urine.

The period of most active experimentation in this whole field may be said to have begun after the establishment of the possibility of surgical removal of the hypophysis in the rat. The hypophysis is so deeply placed within the center of the head that the operation for its removal, hypophysectomy, had usually been done by opening the top of the skull and gently holding the brain aside until the surgeon could dislodge the hypophysis from its own cavity, the sella turcica. This has been done by many notable surgeons—Paulesco of Roumania, Ascoli and Legnani of Italy, Sir Victor Horsley of England, and Harvey Cushing in this country, among others. They had chiefly employed dogs for these operations which had been attended by a high operative mortality. What is worse, there was a high postoperative mortality. Within a day or two the dogs became drowsy and comatose, and, believing that their condition was a peculiar one due only to loss of the pituitary, the term cachexia hypophyseopriva was coined for the stupor into which they fell. We now know that their condition was due to brain injury. In the dog, the one way to avoid brain injury was shown by the Viennese gynecologist Aschner, who reached and removed the pituitary through the roof of the mouth. The lowly rat possesses peculiar advantages, for in it the cavity occupied by the pituitary—the sella turcica—is separated from the cavity occupied by the brain by a fold of the dura mater called the diaphragma sellae, and there is no chance of mechanically disturbing the brain when one enters the sella turcica from below. Furthermore, when the head of these little rodents is so completely thrown back as to rest on its dorsum, one approaches the sella by pushing the pharynx aside. Smith cleverly worked out the parapharyngeal operation in the rat, and, what is more important, did scores of these operations to find that there were always characteristic anatomical changes after the successful removal of the hypophysis. He could establish the fact that he had completely removed the hypophysis by serial section of the whole region of the base of the skull, and when the operation was demonstrably complete, he invariably got subnormality of the thyroids, gonads, and adrenal cortex. It was apparent that these three glands needed their sister gland for their own normal development and function, for in young animals they failed to develop and in adult animals they regressed after the pituitary was removed. If the pituitary is removed on the day of birth of a litter, the mother animal cannot suckle her young even though during pregnancy her mammae have been fully developed and are ready for their duty. The secretion of milk then requires a hormone from the pituitary.

There are other characteristic changes in hypophysectomized animals into which it is unnecessary to go here, but I should like to refer very briefly to them. If hypophysectomy is done in young animals (rats, 1 month of age), the little creatures retain their infantile or youthful pelage—a soft downy hair—and retain their milk dentition. They have almost no muscular tone and are "flabby" when picked up. They have a lowered resistance to infections so that they fall victim to laboratory-animal epidemics of all sorts. Yet if sedulous care is exercised, hypophysectomized animals may actually attain old age for this species, that is, approach the third year of their life. We have had great numbers of them survive for a year. This experience has settled, of course, the query as to whether the hypophysis is actually needed for the continuance of life. Finally, they are in major jeopardy through the withdrawal of food. As is well known, starvation periods of a few days' duration are tolerated by all normal animals, but fatalities often attend the withdrawal of food from hypophysectomized animals within thirty or forty hours, and their death is preceded by hypoglycemic coma. Hypophysectomized animals use up their carbohydrate reserves with alarming speed.

Let us now turn to a short description of each of the internal secretions or hormones which the hypophysis secretes. We are confident that there are six separate hormones. When chemists in conjunction with us began to purify the extracts made from the anterior hypophysis of slaughtered animals, we found that we could restore some of the defective organs and tissues after hypophysectomy without restoring others. We have gradually learned to make six different extracts, each of which now restores a single feature of the hypophysectomy syndrome. Solutions of the pure growth hormone make such animals grow again but they still have atrophic thyroids, gonads, and adrenal cortices. Thyrotropic hormone does not influence their growth—they are still dwarfs—but the thyroid gland now hypertrophies and again secretes thyroxin, yet the gonads and adrenals are still atrophic. I need not continue—these and these alone are the reasons for our believing in the six different substances or hormones. The list attains six because two different materials or hormones, not a single one, appear to control the gonads.

In testing the purity of hypophyseal extracts, it is important to have specific tests for each of the hormones known to be present in extracts of the gland. The purified extract should not be contaminated with any hormones save the one which it contains. In order to establish this lack of contamination, it is essential to administer it at high dosage and for a considerable time. This, however, is the only object requiring high dosage and a long stretch of time. A test for the potency of an extract containing the pure hormone should be effected with low dosage and quickly. If these conditions could not have been met, we could not have assisted our chemists in quick purification of each of the hormones. A word must be said also about the strict electivity of tests. They must be given by one hormone and by it alone.

I shall now present the essential story of the six hormones:

Growth Hormone.—As regards the growth hormone, it has already been explained that continual administration of this substance re-establishes growth

in hypophysectomized animals and, if high dosage be employed, increased growth in normal animals. Gigantism is thus produced. This is easily effected and has been done not only in the rat but also in the dog where we employed a small pure strain—the Dachshund.

We do not test a growth hormone extract by producing giants, for we would thus be at work many weeks or months before we knew the potency of an extract. Fortunately, growth hormone administered to hypophysectomized animals causes an immediate resumption of growth, which is easily indicated by increase in total body weight. Groups of completely hypophysectomized young rats of the same age, sex, and body weight are weighed daily for ten or fourteen days and if no increment in total body weight in excess of 2 or 3 grams is detected, they are judged to be in complete growth stasis. The growth hormone solution of unknown strength is given them subcutaneously or intraperitoneally and at the same hour each day weighings are conducted. Dependent upon the unknown concentration of the growth hormone present in the extract, prompt gain in body weight results—a gain varying from ½ gram daily to several grams daily. If, in a ten-day period, a total gain of 10 grams in body weight (1 gram daily) occurs, we have chosen to designate the daily dose producing this as one unit of growth hormone. A curve may be constructed showing the relation between the weight increases and the logarithms of the doses of growth hormone employed or multiples of a unit dose, and this curve proved to be a straight line within certain limits. A single level of any growth hormone preparation may therefore be injected into an adequate number of standardized test animals and by interpolation in the curve, the unitage of the preparation may be determined. We continually sought some single highly characteristic change produced by the growth hormone and began histological exploration of skeletal changes before announcement was made from Laqueur's laboratory that they also had employed these tests.

Growth hormone stimulates chondrogenesis and osteogenesis immediately, the cartilage change occurring first. We need now only to measure the width of the epiphyseal cartilages to know how much growth hormone has been administered. No other hormone from the pituitary produces these changes. We do not have to cut and stain the beautiful sections now produced in Dr. Hermann Becks' laboratory. We have only to take a single bone—the left tibia, for example—disarticulate it at the knee joint and quickly dissect it free of muscular attachments and fix it in formol, or, if we please, without fixation, split its proximal end in the medial line with a safety razor blade, pour silver nitrate on the split bone, and carry it to the window for the reduction produced by light. Since the epiphyseal cartilage is free of calcium and has been greatly thickened in four days by the growth hormone, we may thrust it under a binocular microscope and measure the width of this cartilage directly with an eyepiece micrometer. The growth hormone is standardized just as easily this way as by measurement of the total increase in body weight, and smaller doses are required to effect changes in the width of the epiphyseal discs than are required for significant weight increases of the whole body.

Thyrotropic Hormone.—High and prolonged dosage with the thyrotropic hormone can convert the atrophic thyroid gland of hypophysectomized animals into a large structure in which the tall columnar cells are festooned into the individual follicles, as is the case in exophthalmic goiter. The epithelium of the vesicles of the thyroid gland of hypophysectomized rats consists of very flattened cells. A unit of the thyrotropic substance or hormone is defined as the amount necessary to convert this squamous epithelium into a low cuboidal structure, the nuclei of which now tend to be spherical rather than flattened, and the cytoplasm also more bulky, vacuoles appearing here and there in the colloid next to the cell.

Gonadotropic Hormone.—The gonads of an hypophysectomized animal of either sex are, in the case of adults, rather completely atrophied, and, in the case of young animals, remain in an infantile state. One group of cells in the gonads, indeed, undergoes characteristic atrophic changes. I refer to the interstitial cells which, whether in ovary or testis, exhibit changes in their nuclei which are so characteristic that one may see them at first glance with low power of any microscope. These shrunken little cells have the chromatin of their nuclei agminated against the nuclear membrane and arranged spokelike toward it. They have consequently been designated "wheel cells" or "deficiency cells."

As is well known, there are two components of the gonads: the first component may be designated the germ-cell-bearing structures, whether ovarian follicles or testicular tubules, the structures which house and nourish the ova and spermatozoa; the second great component consists of the interstitial cells to which reference has just been made. Gonadotropic extracts of the hypophysis can be made to stimulate one of these two major gonadal components and not the other, i.e., some extracts can be made to stimulate, restore, and hypertrophy the interstitial cells without affecting the ovarian follicles. Other extracts can be made to stimulate the growth of the ovarian follicles with their contained ova although the interstitial cells between the follicles remain deficient. The extracts which stimulate the ovarian follicles also stimulate the testicular tubules and promote spermatogenesis without any effect on the testicular interstitial cells. For these reasons the anterior pituitary is now believed to contain two kinds of gonadal stimulants or gonadotropic hormones: the hormone which directly influences the germ-cell-producing component of the gonads has been called the follicle-stimulating hormone, and the hormone which influences selectively the interstitial cells, the interstitial-cell-stimulating hormone. There is some dispute, into which I will not now enter, as to whether both of these hormones are needed in the male, but there is no question that they are needed in the female, for without the interstitial-cell-stimulating hormone the follicle-stimulating hormone can never produce true ripening of the Graafian follicles, their rupture (ovulation), and their conversion into corpora lutea. It is surprising how little of the interstitial-cell-stimulating hormone is required to increase the effects of the follicle-stimulating hormone. So striking is the action together or synergism of these two hormones that we can measure the follicle-stimulating hormone by potentiating

it with a minute amount of interstitial-cell-stimulating hormone. When we select an exq uisitely small dose of follicle-stimulating hormone, so low that it does not cause appreciable growth of the ovarian follicles, and add an equally low dose of interstitial-cell-stimulating hormone, a sudden stimulus is given the follicles to secrete the female sex hormone, estrin, and thus cause the accumulation of fluid and swelling of the uterine horns which we associate with estrus. Finally, we may define a unit of follicle-stimulating hormone as the least amount which will cause the growth of ovarian follicles in hypophysectomized young rats, and a unit of the interstitial-cell-stimulating hormone as the least amount of this substance which will create an observable restitution in the deficient interstitial cells.

Adrenotropic, Adrenocorticotropic, or Corticotropic Hormone.—Mention has already been made of the fact that one of the characteristic sequelae of hypophysectomy, along with thyroid and gonadal atrophy, is atrophy of the adrenal cortex. This becomes a mere shell of tissue, covering the adrenal medulla. Another characteristic change consists in the distribution of the adrenal cortical lipids. When frozen sections are cut of the normal adrenal and sudan III is applied, lipid droplets are seen to be scattered in all three layers of the cortex, glomerulosa, fasciculata, and reticularis. The shrunken adrenal cortex of hypophysectomized rats no longer contains appreciable lipids and the lipids present are confined to the glomerulosa and last portion of the reticularis, leaving a great lipid-free or sudanophobe zone. The adrenotropic hormone of the pituitary when given in high dosage for several days brings about not only a restitution of the defective cortex of hypophysectomized animals but the same distribution of small lipid droplets in all layers of the cortex which characterizes normal animals. The hormone, if long applied, can even bring about hypertrophy of the cortex of either normal or hypophysectomized animals. In order to standardize adrenotropic extracts it is not necessary to cause this hypertrophy or even a complete restitution of the adrenal cortex of hypophysectomized animals. So sensitive is the distribution picture furnished by the adrenal cortical lipids that when this hormone is given, lipids again begin to appear throughout the fasciculata, and the bare beginning of this change can be detected in frozen sections. The slightest amount of the adrenotropic hormone which will accomplish this within a definite time interval may be called a "Repair Unit" of the hormone. To some minds, a more satisfactory unit of the efficacy of this hormone is constituted by the least amount which will restore the adrenal to its normal weight or the least amount which when administered immediately after hypophysectomy will prevent any loss in adrenal weights. This may be designated the "Maintenance Unit."

A few years ago, H. D. Moon of our laboratory discovered that the adrenotropic hormone causes dwarfism; the young animals receiving it failed to grow. This might have been due to toxic substances in the early extracts, but we now know that the same effect is secured with the pure hormone. It causes atrophy of the epiphyseal discs—just the opposite effect from that se-

cured from growth hormone. We can, in fact, in hypophysectomized animals nullify the effects of a given dose of pure growth hormone by simultaneous dosage with the pure adrenotropic hormone. Finally, I should like to refer to another striking action of the adrenotropic hormone which causes atrophy of the thymus and of the lymphatic glands. Indeed, it can be seen to effect the number of circulating lymphocytes within a few hours after its administration. It is a long cry from these findings to the claim that we can cure malignant lymphoid leucemias with this material, but I mention this to you as one of the hopes raised by these experimental findings.

Lactogenic Hormone.—Riddle's discernment that the pituitary substance stimulating the crop glands in immature pigeons was a hormone *sui generis*, not identifiable with the other anterior pituitary hormones, quickly led to investigation of its role in mammalian lactation. It would perhaps be surprising to biologists of a generation ago to learn that the same humoral agent is concerned in the stimulation of two such utterly different organs, one an endodermal, the other a true ectodermal epithelial derivative, but such is the case. Our unit here is the amount of lactogenic hormone required to cause recognizable development of the crop gland when these semitransparent sacs are held to the light for naked-eye inspection. When, instead of injection under the skin or into the pectoralis muscle, the lactogenic hormone is injected into the neck skin against which the crop bellies, very minute amounts of the hormone can be recognized, as Lyons has shown, and by the aid of this test he was able to chart the variable amounts of it in the urine of lactating women and indeed of normal women and men.

Metabolic Effects.—I will conclude my remarks by brief reference to the fact that this little gland, the pituitary, thrusts its ubiquitous finger into some of the intricate chemical machinery of the body—its metabolism. I have told you that hypophysectomized animals should not be starved. A decade ago, Professor Houssay of the Argentine showed us that hypophysectomy would prevent the invariable fatality which follows complete removal of the pancreas, but, if hypophyseal extracts are administered to depancreatized animals, a rapidly fatal diabetes is reinvoked. Just how absence of the hypophysis thus ameliorates an otherwise fatal derangement of carbohydrate metabolism has not yet been determined. I trust that on some future occasion I may have the opportunity to bring to you a clear explanation for Professor Houssay's brilliant discovery. Our first tests, of course, must concern themselves with detecting just which of the pure hormones exert this "diabetogenic" effect.

It is characteristic of science that its task is never finished, and a satisfactory presentation of any field should properly arouse imaginative effort as to how it can be applied and extended. If, in any modest degree, I have thus whetted the appetities of your group, I should deem this the type of reward which every investigator seeks.

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Col. Neal Harper
Col. Wm. H. Siefert
Col. Richard F. Thompson
Col. L. B. Wright

There may be members in the Service whose names do not appear in the above list. These members should notify the secretary at once so that their names may be included.

Max E. Ernst, Secretary, American Association of Orthodontists, 1250 Lowry Medical Arts Bldg., St. Paul, Minn.

Department of Orthodontic Abstracts and Reviews

Edited by

DR. J. A. SALZMANN, NEW YORK CITY

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Study of Congenitally Missing Second Premolars and Space Factors in the Arches: By Clarence P. Oliver, Peter J. Brekhus, and George Montelius. The Dight Institute of Human Heredity and the School of Dentistry, University of Minnesota, Minneapolis, Minn., *J. Dent. Research* **24**: 217-221, October, 1945.

Several theories which have been presented, such as those by Montagu, Schultz, and others, seem to fit special cases but do not account for the congenital absence of teeth located in the premolar region of the arches. Mere chance alone does not explain the failure of some types of teeth to develop. In an earlier publication, the authors called attention to a definite pattern or regularity with which certain teeth failed to develop in 184 persons. They reported that the teeth most frequently congenitally missing were the upper second incisors, second premolars, and third molars. Any other tooth may on occasion be congenitally absent. But except for the lower first incisors the frequency is very low. Since that report, 232 new cases of congenitally missing teeth have been collected and studied. In tabulating the new data we find that the pattern of the congenital absence of teeth remains the same. The upper second incisors, second premolars, and third molars which are most often absent have also been found to be the most variable in pattern and size. It seems justifiable, therefore, to assume that some factor or facors control the variation in the development of these tooth buds.

The authors of this report have suggested that arch size and congenital absence of teeth seem to be separate entities. This contention is also borne out by their study of missing second premolars which is reported in the present paper. All interpretations are based upon examinations of the patients with a study of dental models made from impressions of the arches and complete oral radiographs of those persons.

Among these patients, 176, or 4.8 per cent, lacked one or more teeth or had peg-shaped or supernumerary teeth. Seventy-seven, or 2.1 per cent, of the patients had anomalies of the upper second incisors. Eighty-seven, or 2.4 per cent, were found to have anomalies of the second premolars in one or more of the quadrants. These incidences are higher than the ones reported earlier, and a probable explanation of the low frequencies was given at that time. The general pattern agrees with the one discussed in that report.

Among 427 persons now in their records who have congenital anomalies of the teeth, 162 show anomalies of the second premolars, of which 153 are reported in this study. These 153 persons failed to develop a total of 330 second premolars. In the upper arch 62 were absent in the right portion and 77 in the left. In the lower arch the respective numbers were 87 and 104.

In this same group of persons, 64 had one or more deciduous second premolors at the time they were examined, the number of retained deciduous teeth being 115. In the upper arch, 23 were present in the right and 17 in the left part of the jaw. In the lower arch, 35 remained in the right and 40 in the left.

One of the important functions of the deciduous second premolar is to retain space for its successor, the permanent second premolar. With the early loss of the deciduous tooth, very often the permanent first molar will erupt mesially. When the permanent second premolar is ready to erupt, the space has been filled by the first molar. A rearrangement of the entire dental arch often becomes necessary in order to recreate space for the second premolar. Very often the second premolar is extracted as the lesser of two evils. In persons who never develop the second premolar, the closing of the space may lead to a perfect alignment of the teeth.

The general contention has been that lack of space in or decrease in size of the arches is responsible for the congenital absence of teeth. With this in mind we found it of special interest to observe if loss of space may be a contributing factor in the disappearance of the second premolars in man's dental formula.

Among the 153 persons with congenitally absent premolars, 64 had 1 or more of their decidous molars present with ample space for a permanent tooth to erupt. Although the 89 persons had lost all their deciduous molars, 32 still had ample space for a permanent premolar in one or more of the quadrants. In 21 cases, the retained space was less than enough to accommodate the permanent tooth, and in 36, the space between the first premolar and the first molar was closed. In these persons, therefore, 96 out of 153, or approximately 63 per cent of the persons, had no space between the first premolar and the first molar. In some instances one person had a retained deciduous tooth or full space in one quadrant and only a partial space or no space at all in another quadrant.

DISCUSSION

The evidence reported in this study substantiates the belief that lack of space in the arches is not a factor in the congenital absence of the second premolars. The greater proportion of persons who lacked those teeth retained the larger deciduous teeth or had ample space for the permanent teeth in one or more of the quadrants. A single individual who congenitally lacks all four permanent second premolars sometimes will retain a deciduous tooth in one quadrant, have ample space in another, and lack space in still another. Where the deciduous tooth is not retained, the amount of space between the first premolar and the first molar probably is determined by the age at which the deciduous second molar was lost. An effect of age at extraction of first molars on the amount of space between the premolars has been reported by Salzmann.

Accident alone cannot account for the congenital absence of teeth. If that were true, all tooth germs should be affected with equal frequency. We have ample evidence that this does not occur. Certain types of teeth are seldom congenitally absent. Others, namely the third molars, upper second incisor, second premolars, and to a lesser extent lower first incisors, are frequently missing. This pattern occurs with a regularity which suggests an orderly process associated with the congenital loss of the teeth.

The factor responsible for the congenital absence of one type of tooth will probably explain most of the absences of the other types as well. Second premolars, which are in the midportion of the arches quite removed from anatomical structures associated with the incisors or third molars, are missing almost as frequently, if not as frequently, as the upper second incisors. It seems probable, therefore, that the factor responsible for the congenital loss of teeth controls

the development of the dental buds, possibly the rate of development, regardless of the position in the arch. Certain buds are more likely to be affected by this modified development than are other buds.

A brief report is made on the incidence of congenitally missing teeth in 2,699 persons. The conditions observed in persons lacking second premolars are discussed.

Among 153 persons with congenitally missing second premolars, 330 of the premolars failed to develop. In these persons, 115 deciduous second molars were present at the time of examination.

Deciduous teeth were present or ample space still remained in one or more quadrants of 96 of the 153 persons who lacked second premolars. Of the others, 36 had no space and 21 had only slight space between the first premolar and first molar.

It is concluded that lack of space in the arches cannot account for the congenital loss of second premolars. It is suggested that the factor causing the loss of these teeth probably controls the development of the dental buds, and that the same factor effects the loss of the other kinds of teeth which are frequently missing.

Archie B. Brusse

American Association of Orthodontists

THE PRESIDENT'S PRECONVENTION LETTER

The American Association of Orthodontists was one of the first organizations voluntarily to cancel its national meeting under Mr. Byrnes' memorandum placing a wartime ban on conventions. This was soon after the Battle-of-the-Bulge had started in Europe, and the military heads were predicting the end of the war in Europe within two years and victory over Japan in five years. Little did we think at that time that we would be arranging a meeting for the fall of 1946, but V-E and V-J days arrived much sooner than had been predicted.

After making tentative arrangements for a meeting in May, 1946, the Committee contacted the Office of Defense Transportation and the Secretary of the American Hotels Association, and were advised that these two groups would not even consider discussion of large national conventions before the fall of 1946.

During the first six months following V-J day, the already overcrowded travel and housing facilities were further swollen far beyond normal capacity by soldiers and sailors returning from every battlefront in the world. The congestion was so great on both the East and the West Coasts that returning military personnel were kept on the ships as long as ten days or two weeks after they reached their home port, because the trains could not transport them and the cities could not house them. It was not possible at that time to accomplish even our duty toward our returning servicemen, and to plan a national meeting was beyond consideration. Before this congestion could be cleared away, the 1946 summer tourist travel was under way.

We could not postpone the meeting of the American Association of Orthodontists indefinitely. It was necessary that we get it off the calendar. St. Louis was considered as a central meeting place, but, like in every other large city in the United States, the hotels were not interested in conventions. The question was one of expediency, and the time and place of the meeting could not be considered for the convenience of each individual group.

The Broadmoor Hotel at Colorado Springs had a $1,000,000 building program on architects blueprints in the fall of 1945, and the Platt Rogers Construction Company expected to complete the contract early this summer. The Broadmoor management promised us adequate space to accommodate our members if the personnel quarters and the two apartment buildings under construction were complete at the time of our meeting. But you know the answer. Industrial strikes have curtailed building materials and labor, and it is now doubtful if the Broadmoor will have any additional accommodations until 1947.

Mr. J. V. Hawkins, manager, and Mr. W. Henry Willie, assistant manager, of the Broadmoor Hotel, have been very gracious and cooperative, giving unlimited time in an effort to help us find a happy solution to our housing problems. They have done everything possible—sometimes "beyond the call of duty." But we realize that there is a limit to the number of persons even a hotel like the

Broadmoor can accommodate. We appreciate their having arranged for and confirmed reservations for 300 of our members.

The Antlers Hotel, too, has been very cooperative, having advanced to the following week another large convention which has been booked for the same dates, in order to accommodate our Association members who were not able to make reservations at the headquarters hotel.

Reservations confirmed up to the present time indicate that the attendance at Colorado Springs will far exceed that of our Chicago meeting, which was the largest in the history of the Association. It is necessary, as it was at Chicago, to find housing for some of our members in hotels other than the headquarters hotel. Many of you have perhaps planned to stay at the Broadmoor and will be somewhat disappointed at not being able to secure accommodations there. But you will find the Antlers Hotel to be one of the finest in the country, with excellent service, and conveniently located to downtown Colorado Springs and transportation to all points of interest in the region. Adequate transportation will be provided between the Antlers and the Broadmoor Hotels during the meeting.

In addition to these two hotels there are several modern auto courts at Colorado Springs, which may be preferred by those who travel by private auto. For further information about these auto courts, contact Dr. Oliver H. Devitt, Chairman of Local Arrangements, 523 Republic Building, Denver 1, Colorado.

The Program Committee, under the able chairmanship of Dr. Wm. R. Humphrey, has done a splendid job in arranging for us a unique and exceptionally interesting scientific program. The Pacific Coast Society meeting was canceled because of the recent railroad strike, and, as an alternative, that group joined forces with our Program Committee to collaborate on a special Pacific Coast Society Day, with Dr. J. Camp Dean, President of the Pacific Coast Society, presiding and supplying the program talent for the day. Arrangements have been made also for a Rocky Mountain Society Day, with Dr. Henry F. Hoffman, President of the Rocky Mountain Society, presiding, and for a Southwestern Society Day, with Dr. Brooks Bell, President of the Southwestern Society, presiding for the day. The Committee has eliminated general clinics and has substituted lecture clinics instead.

All of us who have traveled during the past year are familiar with the usual inconveniences in travel and hotel accommodations, due to conditions of a postwar reconstruction period. Those who stop even at the best hotels must often wait a few hours for rooms to be prepared, or wait their turn for other small services. The hotels may not have sufficient personnel to render the usual detailed and thoughtful western hospitality. But we feel that Colorado Springs and the Pikes Peak region offer many diversions and attractions that will by far offset any inconveniences the members may encounter while there. If you come to the meeting with a tolerant attitude toward these small annoyances, your visit will be a pleasant one.

The committees have done all that was possible under existing conditions to make this a gathering that will be long and happily remembered.

Archie B. Brusse.

News and Notes

TENTATIVE PROGRAM FOR THE MEETING OF THE AMERICAN ASSOCIATION OF ORTHODONTISTS IN COLORADO SPRINGS, COLORADO

SEPT. 30, OCT. 1, 2, 3, 1946

Monday, Sept. 30, 1946

ROCKY MOUNTAIN SOCIETY OF ORTHODONTISTS DAY

Henry F. Hoffman, President of the Rocky Mountain Society, presiding

MORNING:

9:00 Invocation.
Address of Welcome. Lester C. Hunt, D.D.S., Governor of the State of Wyoming.
Response to Address of Welcome. Earl G. Jones, President-Elect, Columbus, Ohio.

9:15 President's Address. Archie B. Brusse, Denver, Colorado.

9:45 The Evolution and Devolution of the Human Face. Ernest A. Hooton, Professor of Anthropology, Harvard University.

11:00 "Use of the Twin Arch Mechanism in the Treatment of Cases in Which Extraction Is Indicated." Joseph Johnson, Louisville, Kentucky.

12:00 Luncheon.

AFTERNOON:

Lecture Clinics (clinics will be repeated three times during the afternoon).

"Removable Appliance." S. D. Gore, New Orleans, Louisiana.

"Tooth Positioner." Harold D. Kesling, La Porte, Indiana.

"Longtube X-ray Technic." Gordon Fitzgerald.

Tuesday, Oct. 1, 1946

PACIFIC COAST SOCIETY OF ORTHODONTISTS DAY

J. Camp Dean, President of the Pacific Coast Society, presiding.

MORNING:

9:00 "The Limitations of Orthodontic Treatment." Part 2, "Permanent Dentition Diagnosis and Treatment." Hays N. Nance, Pasadena, California.
(Part 1 was read before the Southern Society of Orthodontists on Jan. 28, 1946.)
"Gnathostatic Diagnosis." Will G. Sheffer, San Jose, California.
"The Principles and Mechanics of Treatment With the Sliding Twin Section Appliance." Clarence Carey, Palo Alto, California.

12:00 Round Table luncheon presided over by George W. Hahn, Berkeley, California (who will be remembered for the way in which he conducted the symposium at the Chicago meeting).

Following luncheon there will be an afterluncheon speech by Spencer Atkinson, Pasadena, California, entitled "History, Trends, and Future of Orthodontics."

Wednesday, Oct. 2, 1946

SOUTHWESTERN SOCIETY OF ORTHODONTISTS DAY

Brooks Bell, President of the Southwestern Society, presiding.

MORNING:

9:00 "Development of the Mandible." Henry Sicher, Chicago, Illinois.
11:00 "Anthropometry and Orthodontia." Ernest A. Hooton, Harvard University.
12:00 Luncheon

AFTERNOON

2:00 Lecture Clinics (clinics will be repeated twice during the afternoon).
"Labial Lingual Arch Technic and the Guide Plane."
Oren Oliver, Nashville, Tennessee.
Russell Irish, Pittsburgh, Pennsylvania.
"Edgewise Mechanism."
Edward Arnold, Houston, Texas.
A. P. Westfall, Houston, Texas.
Bert Gaylord, Dallas, Texas.
C. G. Rowland, San Antonio, Texas.

Thursday, Oct. 3, 1946

MORNING:

9:30 Research Section, under the direction of Allan G. Brodie, Chicago, Illinois.
10:00 Prize Essay.
11:00 Business Meeting.

American Association of Orthodontists

The next meeting of the American Association of Orthodontists will be held at the Broadmoor Hotel, Colorado Springs, Colorado, Sept. 30, Oct. 1, 2 and 3, 1946. Members of the American Dental Association are invited to attend this meeting. Proper credentials should be obtained in advance from the secretary of the American Association of Orthodontists or from the secretary of a constituent society.—MAX E. ERNST, Secretary, 1250 Lowry Medical Arts Bldg., St. Paul 2, Minn.

Change in Meeting Place, American Board of Orthodontics

The headquarters of the American Board of Orthodontics has been changed from the Broadmoor Hotel to the Antlers Hotel in Colorado Springs.

This announcement has just come to the Editor's desk from the Secretary of the American Board of Orthodontics and should be noted carefully by all those expecting to appear before the Board.

Koshare Indian Dancers at Meeting of American Association of Orthodontists

At the annual meeting of the American Association of Orthodontists at the Broadmoor Hotel, Colorado Springs, Colorado, on Sept. 30, Oct. 1, 2, 3, 1946, orthodontists will enjoy a rare treat.

The famous Koshare Indian Dancers will give an exhibition of their art and skill in the background and stage setting of the grounds of the colorful Broadmoor Hotel.

The Koshare Indian Dancers will ask you "to listen to the rhythm of their Great Drum; feel it as it throbs in your hearts. Let your tired minds relax to the soothing beat of the Great Medicine Drum; see again the carefree life of the Red Men as the Koshare reveal the age-old scenes of their Happy Hunting Ground.

"Follow them on the hunt of the shaggy buffalo, through the Valley of the Winding Waters in search of game. Forget those whom you may know in this group, but live with them the life of the great people they represent. Enter into the rhythms of the Great Drum. Let your hearts dance free with the winds of Shadowland. Look far into the Turquoise Sky and see the Great Thunder Bird and remember that there lives Waconda Agua, the Great Spirit. May he fill your hearts with the peace of the Forest Children."

All this you will see as a part of the colorful entertainment program at Colorado Springs.

New York Society of Orthodontists

The next meeting of the New York Society of Orthodontists will be held at the Waldorf-Astoria Hotel, New York, on Monday and Tuesday, Nov. 4 and 5, 1946.

Pacific Coast Society of Orthodontists

NORTHERN SECTION

The Northern Section of the Pacific Coast Society of Orthodontists held its meeting on Thursday, April 11, 1946, in Portland, Oregon. The meeting began with an eight o'clock breakfast at the Heathman Hotel. The program and business sessions were held in the Auditorium of the Medical Dental Building, Dr. E. B. Faxon presiding.

Members present: Drs. M. H. Fisher, W. P. Dinham, P. T. Meaney, A. E. Stoller, J. E. Richmond, Wm. P. McGovern, H. N. Moore, D. C. MacEwan, Geo. A. Barker, E. B. Faxon, E. A. Bishop, S. B. Hoskins, J. J. Frazier, P. D. Lewis, E. W. Tucker, Wm. F. Clarke, and H. G. Stoffel.

Guests present: Dr. Ben Nickalls of Victoria, British Columbia, Dr. A. S. Maxon of Walla Walla, Washington, Dr. Ralph Cooper of Portland, Dr. R. O. Gothenquist of Seattle, and Dr. Geo. McCullock of Yakima.

The Northern Section voted to hold its next meeting in Seattle. Dr. Paul Lewis was elected chairman of the Section and Dr. A. E. Stoller was elected Secretary-Treasurer.

The program began with a paper by Dr. Margaret Ringer, phonetician, on "Some Physiological Considerations in the Use of Swedish Type Obturator," illustrated by a presentation of slides, motion pictures, and phonograph records.

Dr. Ben Vidgoff, endocrinologist in practice and with the University of Oregon Medical School, presented a paper with case histories on "The Place of Endocrinology in Orthodontics." Dr. W. R. Dinham gave the dental case histories of the patients.

Dr. W. R. Dinham introduced to the section the use of the Wetzel Grid-graph for Evaluating Physical Fitness as presented by Drs. Wendell Wylie and Johnson at a recent Angle meeting in San Francisco.

The program was completed with table clinicis presented by Drs. Don MacEwan, Paul Lewis, Emery Frazier, Wm. McGovern, M. H. Fisher, and E. A. Bishop.

CENTRAL SECTION

The Central Section of the Pacific Coast Society of Orthodontists held its quarterly dinner and business meeting at the Alexander Hamilton Hotel in San Francisco on May 7, 1946. The meeting was called to order by Dr. C. W. Carey, Chairman.

Members present: Drs. Reuben L. Blade, J. Camp Dean, C. W. Carey, Harold H. Bjornstrom, Seymore B. Gray, Wendell I. Wylie, E. F. Lussier, Fred Wolfsohn, Will Sheffer, Cecil Rand, George W. Hahn, L. E. Carter, William S. Smith, Ernest L. Johnson, Allen E. Scott, Ray McClinton, Howard Dunn, Walter J. Straub, and Arthur F. Skaife.

Guests present: Drs. R. Curtner, Grenfell, Farr, Howard Jan, Ben Ledyard, Arnold W. Weiser, Harry S. Thompson, J. Gazola, Ray Brownell, and R. Railsbach.

A program on the "Treatment of the Mixed Denture Stage" was presented in interesting short papers by Drs. J. Camp Dean, Fred Wolfsohn, George W. Hahn, and Will Sheffer, followed by an informal discussion by the membership.

New Dental Corps Draft

Subsequent to the close of actual fighting in the war, the Army Dental Corps found itself in an undesirable position in regard to replacements. It had recruited many men from private dental practice to serve in the Armed Forces during the war, and when the war was over and these men rightfully should have been discharged, it was discovered that there were no replacements available for this purpose. Consequently, many men had to remain in the Service who had a right to discharge. Upon the realization of the importance of this situation, the Army sent out officers to visit all of the larger dental schools and address the senior classes who were then about to graduate. The students were urged to apply for commissions in the Army Dental Corps and it was explained that the situation was critical. However, as a result of this effort, there were very few applications forthcoming for commissions in the Corps from the recent graduates in dentistry.

Since replacements were not available for veterans of the Dental Corps, the War Department then requested the Selective Service to induct 1,500 dentists as replacements for the Army Dental Corps. It is obvious that the only available dentists within the age bracket that could be used for this purpose would be recent graduates of the dental schools. It seems, too, that the majority of these recent graduates were at one time or another during their school terms subsidized by the government through the agency of the various military programs, such as the A.S.T.P., Army, and V-12, Navy.

This seems to be, in short, the reason why Selective Service is now processing these eligible nonfather dentists for induction into the Army. It is understood, however, that the fact that they are drafted does not preclude them from immediately applying for a commission in the Army Dental Corps. In fact, that seems to be the over-all plan.

The Army obviously desires that these inductees apply for a commission promptly, inasmuch as it is plain that these men will be of no service to the Army as dentists if they are allowed to remain in the ranks as privates. These nonfathers are permitted to make application for a commission to the office of the Surgeon General or to a recruiting station, whichever is more convenient. In the event that these men wait until they are ordered for induction, then they must make application after they enter the Army as privates. This plainly means that such men will be compelled to serve as privates until their papers are processed before they are finally commissioned.

It is estimated that there are approximately 67,000 dentists now practicing in the United States and of this number 24,500 have served in the Army, Navy, Public Health Service, or Veterans' Administration. There were about 25 per cent of the available dentists in the age bracket, 21 to 40, who were rejected for physical disabilities. Accordingly, with the percentage of 67,000 being 50 per cent over the age of 50, it is plain why there is such a scarcity of trained men for the Armed Services.

It is to be noted that the Regular Navy Dental Corps authorized by law is 1,200 and that for the Army is 1,400 dentists, and that at this time the Navy has a little more than 400 in the regular Navy Dental Corps and the Army about 270. This does not include those who are leaving the regular service because of retirement or disability or for other reasons, therefore it is apparent that if the regular Dental Corps of the Army and Navy are to be filled to their capacities, it will require over 2,000 dentists who mean to make either the Army or Navy their career. In addition to this, the authorized strength of the Army, Navy, and Marine Corps combined, as of July 1, 1946, is 2,716,000 officers and men, which brings about a total of 5,432 dental officers needed for an armed force of this size. Therefore, there will have to be approximately 2,500 dentists on duty who are reserve officers in addition to the Regular Dental Corps. This is based upon the ratio of two dentists per 1,000 officers and men.

This brings about a problem, again, in the profession. In view of the fact that at the present time even with the capacities of the dental schools completely filled, the number of graduates when offset to those leaving the profession by death, retirement, etc., still leaves insufficient dentists. The problem is not a new one, however, as it was called to the attention of the Surgeon General's Office in 1942. Throughout the war, dentists have been deferred in civil life but it has been possible to keep all the dental schools running at full capacity by deferments, in order that not a single dental school would be closed. Now, however, the problem is still a very pressing one, inasmuch as the Veterans' Administration and the Public Health Service will also require the appointment of several hundred men. These latter appointments are permanent and for the duration of professional life, therefore they are drawn from the civilian potential of dental man power.

This seems to add up to the fact that there is a definite shortage of dentists, and that this situation will continue for some time in the future. For ten years prior to the War, it has been pointed out that there were 500 more dentists who either died or discontinued practice than graduated from all the dental schools combined.

Dentistry at this time plainly is badly in need of a campaign to recruit high-type, well-educated young men to enter the profession and increase its man power up to normal strength for the requirements to fulfill its recently acquired obligations.

Reports indicate at this time that dental schools this fall will be filled to capacity, mostly with G. I.'s going to school under the Bill of Rights, and no doubt this situation will continue for several years in the future.

The draft of 1,500 dentists, it seems, is an emergency measure to supply the Armed Forces with dentists, and while quite a shock to young men who have opened up offices and purchased their equipment, none the less, coming immediately subsequent to graduation, it has important compensations for the young dentist. The experience will be invaluable as a practical internship by which he will learn much about practical dentistry that will be of value in the years ahead. In addition, he will be proud of his contribution to the Armed Forces and particularly to the veterans.

Surgeon-General Kirk emphasized that there must always be enough dentists in the service to insure that the health of soldiers will not be jeopardized. Further, he said, if more dentists should become necessary in the future, additional calls for them may be made on Selective Service.

Civilian Institutions Will Profit From Army Psychiatric Experiences

"Civilian institutions can profit by the gains made by the Army in the field of psychiatry," Brigadier General William C. Menninger, Director of the Neuropsychiatry Consultants Division, said recently in a statement on the experiences of the Army with nervous and mental cases in World War II.

Two major innovations in Army treatment of neuropsychiatric cases have been psychotherapy under sedation and group psychotherapy.

By applying the psychiatric lessons learned in recent years, the industrial, educational and criminal institutions of the country and society in general can derive tremendous benefits, according to General Menninger.

In order to capitalize on these advances, however, there must be a wider dissemination of this knowledge among the practicing physicians in this country and more workers must be attracted to the field of psychiatry. Major changes must also be made in medical education if full results are to be attained, General Menninger added.

The marked strides made in neuropsychiatry, which represent one of the major achievements of the Medical Department, were made possible through the skill and knowledge of many of the nation's outstanding psychiatrists, who were marshaled together by The Surgeon General's Office to collaborate in the treatment and prevention of neuropsychiatric cases at a time when there were more cases of this type than medical science had ever dealt with before.

The size of the problem is indicated in the fact that 314,500 men had been discharged by July 1, 1945, for neuropsychiatric causes. This figure represents 43 per cent of the soldiers discharged for medical reasons. In addition, there were 130,000 more men discharged because of personality defects which made them unsuitable for the Army. The picture becomes even darker, considering that out of 4,650,000 men rejected for all causes, 1,825,000, or 39 per cent, were rejected for some type of personality disorder.

General Menninger said that a majority of these discharged soldiers will be able to make a normal adjustment in civilian life. Surveys have shown that most of them are able to adapt themselves to their respective communities and are able to hold down jobs again. Satisfaction in work and play, security and understanding on the part of family and friends provide the best medicine for these veterans.

Through its wide experience with neuropsychiatric cases in this war, the Army developed methods of treatment which proved effective in caring for the soldiers suffering from mental and nervous disorders.

The stress of combat produced a large number of what the Army calls "combat exhaustion cases." From 30 to 40 per cent of these soldiers were salvaged by psychiatric treatment in the first two days close to the front lines, while an additional 20 per cent were made fit for duty in from 5 to 8 days at an improvised unit called the exhaustion center.

In psychotherapy under sedation, which is sometimes referred to as narcosynthesis, narcoanalysis, abreaction and hypnoanalysis, the patient is given an intravenous dose of

a sedative drug, bringing him to a state of semistupor in which he is encouraged to talk and relive the emotional experiences which helped bring about his condition. Frequently these patients could not talk about these experiences before the treatment and often did not remember them. With the help of a skilled psychotherapist, the patient is given "free and adequate drainage" for his emotional tension, which is a factor in his recovery.

The Army has also found that with the proper handling of a case, good results may be obtained when a man is hypnotized and an "emotional catharsis" is produced similar to the results obtained when the drugs are used.

The increased use of group psychotherapy constitutes the second outstanding development in psychiatric treatment during the war. Under the leadership of a psychiatrist, a group of patients with similar problems meet an hour a day for 10 to 30 discussions. The groups are usually from about 15 to 25 men. The patients, under the leadership of a skilled therapist, compare experiences, discuss their problems, and through the insight gained in their cases good results are obtained in a fair percentage of patients treated in this manner.

General Menninger pointed out that the Army's experiences in the Medical Department provide convincing proof that the modern physician must become acquainted with psychological medicine and the dynamics of personality adjustment, as well as with the physical aspects of medical practice.

Recent surveys in wards treating patients suffering from heart disease and gastrointestinal trouble showed that in as high as 41 per cent of the cases there was no organic trouble. The emotional maladjustment of the patients often leads to the malfunctioning of certain organs of the body.

Since the patients in a hospital represent a fairly well-sifted group, it may be assumed that the percentage of such cases in the dispensaries where soldiers first go on sick call would be much higher.

The same can be said about complaints of civilians. The organs of the body act as mirrors for the emotional maladjustments of civilians as well as soldiers. Headaches, pains in the back, heart disturbances, and other symptoms frequently represent no organic trouble, but they are just as much of a problem to the individual and just as painful as disorders due to organic causes.

General Menninger explained that it is not difficult for a person to understand that blushing is a physiological change due entirely to emotion. Just as emotion can produce a change in the color of the face, it also can bring about functional changes in the heart, the stomach, and other organs.

The psychiatrist is concerned with the treatment of cases suffering from functional disorders due to emotional tension, but if doctors generally had a better understanding of the principles involved in this work, tremendous benefits would be derived by civilians in all walks of life.

The role of emotional factors in such cases represents one of the most promising areas of research with perhaps the largest reward in results of any group of problems in medicine. A major step forward will be the joint approach of the internist and the psychiatrist, according to General Menninger.

Notes of Interest

John M. Griffin, D.D.S., announces the association of Townsend B. Paul, D.D.S., recently returned from duty with the United States Navy, in the exclusive practice of orthodontics, 201 North El Molino Avenue, Medical Arts Building, Pasadena 4, California.

Dr. Sidney I. Kohn announces that he has returned from military service and has resumed practice at the Trust Company of New Jersey Building, 35 Journal Square, Jersey City, New Jersey. Practice limited to orthodontics and dentistry for children.

Leo B. Lundergan, D.D.S., announces his return from military service and the resumption of orthodontic practice, Lister Building, 4500 Olive Street, St. Louis, Missouri.

Albert Leon Miller, D.D.S., after sixty-two months of military duty, is now associated with Leonard T. Walsh, D.D.S., 442 Thatcher Building, Pueblo, Colorado. Practice limited to orthodontics. Dr. Miller formerly practiced in Kansas City, Missouri.

Dr. Phelps John Murphey has returned from military duty and has resumed the practice of orthodontics, Fairmount at Welborn, Dallas, Texas.

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The AMERICAN JOURNAL OF ORTHODONTICS AND ORAL SURGERY is the official publication for the American Association of Orthodontists and the following component societies. The editorial board of the AMERICAN JOURNAL OF ORTHODONTICS AND ORAL SURGERY is composed of a representative of each one of the component societies of the American Association of Orthodontists.

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In the January issue each year, the AMERICAN JOURNAL OF ORTHODONTICS AND ORAL SURGERY will publish a list of all of the orthodontic societies in the world of which it has any record. In addition to this, it will publish the names and addresses of the officers of such societies.